PB91-143396

Drinking Water Criteria Document for Dichloroethylenes (1,1-Dichloroethylene), (cis-1,2-Dichloroethylene), and (trans-1,2-Dichloroethylene)

Life Systems, Inc., Cleveland, OH

Prepared for:

Environmental Protection Agency, Washington, DC

19 Dec 90

U.S. Department of Commerce
National Technical Information Service
NTIS

PB91-143396

CRITERIA DOCUMENT
FOR THE
DICHLOROETHYLENES

(1,1-Dichloroethylene)
(cis-1,2-Dichloroethylene)
(trans-1,2-Dichloroethylene)

Criteria and Standards Division
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, D.C.

December 19, 1990

PB89-192512/AS (replace this for old document)

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing

1. REPORT NO.	2.	3. PB91-143396
4. TITLE AND SUBTITLE Drinking Water Criteria Document for Dichloroethylenes		5. REPORT DATE Dec 1990 6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) Criteria and Standards Division		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Criteria and Standards Division Office of Drinking Water Washington, DC 20460		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Office of Drinking Water Criteria and Standards Division Washington, DC 20460		13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE
15. SUPPLEMENTARY NOTES This document is to supersede old document PB89-192512/AS		

16. ABSTRACT

This document deals with the drinking water health effects of Dichloroethylenes through the review of several studies. These studies include animal and humans. Physical and chemical properties are discussed. Carcinogenicity of the compound is reviewed and evaluated through various studies. Any existing guidelines and standards are presented.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
health effects, drinking water, animal studies, cancer risk, cancerous, criteria standards, criteria document, human studies, Dichloroethylenes		

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES 214
	20. SECURITY CLASS *(This page)*	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

FOREWORD

Section 1412(b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish maximum contaminant level goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems.

The Maximum Contaminant Level Goal is non-enforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water. This document provides the health effects basis to be considered in establishing the Maximum Contaminant Level Goal. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and mechanisms of toxicity were evaluated. Specific emphasis is placed on literature data prviding dose-response information. Thus, while the literature search and evaluation performed in support of this document was comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature search in support of this document includes information published up to October, 1980; however, more recent information may have been added during the review process.

When adequate health effects data exist, Health Advisory values for less than lifetime exposures (One-day, Ten-day and Longer-term, approximately a 7-year exposure) are included in this document. These values are not used in establishing the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

Michael B. Cook
Director
Office of Drinking Water

PREFACE

This document was prepared for the Criteria and Standards Division, Office of Drinking Water of the U. S. Environmental Protection Agency, Washington, D. C. under Contract 68-02-3659, Work Assignment 02. The EPA Project Officer was Dr. Edward V. Ohanian. The EPA Lead Reviewer was Dr. Charles O. Abernathy.

Dr. John P. Glennon, ICAIR Systems Division, Life Systems, Inc. was the Task Manager for this study. The principal authors of the document, in alphabetical order, were: Dr. F. Peter Guengerich, Dr. Curtis Klaassen and Dr. Joel Lantz. Dr. David Jenkins was responsible for technical editing and consolidation functions.

TABLE OF CONTENTS

Page

I. Summary I-1-2

II. General Information and Properties II-1-7

III. Kinetics III-1-36

IV. Sources of Human Exposure IV-1-15

V. Health Effects in Animals V-1-56

VI. Health Effects in Humans VI-1-3

VII. Mechanism(s) of Toxicity VII-1-14

VIII. Quantification of Toxicological Effects VIII-1-30

IX. References IX-1-14

LIST OF TABLES

No.	Title	Page
II-1	Summary of Dichloroethylene Concentrations in Finished Drinking Waters at Ten Areas of the United States	II-7
III-1	Correlation of Physical and Chemical Caracteristics to Inhalation Absorption and Distribution of Dichloroethylenes	III-2
III-2	Relative Amounts of ^{14}C in Tissues 72 Hours After Exposure to 10 or 200 ppm [^{14}C]1,1-Dichloroethylene for 6 Hours	III-5
III-3	Metabolism of [^{14}C]1,1-DCE and Covalent Binding of ^{14}C to Rat Hepatic Tissue After Inhalation Exposure to 10 or 200 ppm of [^{14}C]1,1-Dichloroethylene	III-7
III-4	Relative amount of ^{14}C in Tissues 72 Hours After a Single Oral Dose of 1 or 50 mg/kg of [^{14}C]1,1-Dichloroethylene	III-8
III-5	Metabolism of [^{14}C]1,1-DCE and Covalent Binding of ^{14}C to Rat Hepatic Tissue 72 Hours After a Single Oral Dose of [^{14}C]1,1-Dichloroethylene	III-10
III-6	Metabolism and Disposition of [^{14}C]1,1-Dichloroethylene in Rats	III-18
III-7	Disposition of [^{14}C] Following Inhalation of 10 ppm 1,1-Dichloroethylene Over a 48 Hour Period	III-21
III-8	Covalently Bound ^{14}C in Rat and Mouse Following Exposure to 10 ppm [^{14}C]1,1-Dichloroethylene	III-22
III-9	Relative Proportion of [^{14}C] Excretory Products After Oral Administration of 50 mg/kg of [^{14}C]1,1-Dichloroethylene to Rodents	III-23
III-10	Effects of Inducers and Inhibitors of Microsomal Enzymes on Rats of Metabolism of 1,1-Dichloroethylene	III-25

LIST OF TABLES (Continued)

No.	Title	Page
III-11	First-Order and Zero-Order Metabolic Elimination of Dichloroethylenes from a Closed Exposure System: Saturation Points (SP) and Metabolic Rates Expressed as V_{max} and Clearance, Based on 1 kg Body Weight	III-30
III-12	Inhalation Kinetic Constants for the Metabolism of Dichloroethylenes Determined Using Gas Uptake Measurements	III-34
IV-1	Total Estimated Cumulative Population (in Thousands) Exposed to 1,1-Dichloroethylene in Drinking Water Exceeding the Indicated Concentration	IV-3
IV-2	Estimated Drinking Water Intake of 1,1-Dichloroethylene	IV-4
IV-3	Estimated Respiratory Intake of 1,1-Dichloroethylene	IV-7
IV-4	Estimated Intake of 1,1-Dichloroethylene from the Environment by Adult Males in ug/kg/day (% from Drinking Water)	IV-8
IV-5	Total Estimated Cumulative Population (in Thousands) Exposed to 1,2-Dichloroethylenes in Drinking Water Exceeding the Indicated Concentration	IV-11
IV-6	Estimated Drinking Water Intake of 1,2-Dichloroethylenes	IV-13
IV-7	Estimated Respiratory Intake of cis-1,2-Dichloroethylene	IV-16
IV-8	Estimated Intake of 1,2-Dichloroethylenes from the Environment by Adult Males in ug/kg/day (% from Drinking Water)	IV-17
V-1	Acute Toxic Effects of Dichloroethylenes	V-2
V-2	Results of Various Pretreatments on 1,1-Dichloroethylene Effects in Rats	V-17
V-3	Effect of Different Tissues on the *In Vitro* Bacterial Mutagenicity of 1,1-Dichloroethylene	V-27

LIST OF TABLES (Continued)

No.	Title	Page
V-4	Effect of Drug Treatment of Rats on Liver S-9 Mediated Bacterial Mutagenicity of 1,1-Dichloroethylene	V-28
V-5	Dosage, Survival and Mean Body Weights of Rats Administered 1,1-Dichloroethylene by Gavage for 14 Days	V-33
V-6	Dosage, Survival and Mean Body Weights of Mice Administered 1,1-Dichloroethylene by Gavage for 14 Days	V-34
V-7	Dosage, Survival and Mean Body Weights of Rats Administered 1,1-Dichloroethylene by Gavage for 13 Weeks	V-36
V-8	Dosage, Survival and Mean Body Weights of Mice Administered 1,1-Dichloroethylene by Gavage for 13 Weeks	V-37
V-9	Incidence of Liver Lesions in Rats and Mice Administered 1,1-Dichloroethylene by Gavage for 13 Weeks	V-39
V-10	Kidney Adenocarcinomas in Swiss Mice Exposed to 1,1-Dichloroethylene via Inhalation	V-45
V-11	Incidence of Mammary Adenocarcinomas in Female Swiss Mice Receiving 1,1-Dichloroethylene via Inhalation	V-46
V-12	Incidence of Mammary Tumors in Sprague-Dawley Rats Inhaling 1,1-Dichloroethylene	V-47
V-13	Incidence of Tumors in Rats Inhaling 1,1-Dichloroethylene	V-49
V-14	Grossly Observed Tumors in Sprague-Dawley Rats Inhaling 1,1-Dichloroethylene	V-50
V-15	Tumor Incidence in BDIV Rats Treated Weekly with 1,1-Dichloroethylene	V-52
V-16	Grossly Observed Tumors in Sprague-Dawley Rats Given 1,1-Dichloroethylene in Drinking Water	V-53
V-17	Summary of Results from Carcinogenicity Studies with 1,1-Dichloroethylene	V-56

LIST OF TABLES (Continued)

No.	Title	Page
VII-1	Measure of Hepatotoxicity to Rats from Exposure to 1,1-Dichloroethylene and 1,2-DCEthane	VII-10
VII-2	Antagonistic Effects of a Combined 1,1-Dichloroethylene and 1,2-DCEthane Exposure on Nephrotoxicity	VII-12
VIII-1	Summary of Results from Carcinogenicity Studies with 1,1-Dichloroethylene	VIII-20
VIII-2	Summary of Quantification of Toxicological Effects for 1,2-Dichloroethylene	VIII-26
VIII-3	Summary of Quantification of Toxicological Effects for cis 1,2-Dichloroethylene	VIII-27
VIII-4	Summary of Quantification of Toxicological Effects for trans-1,2-Dichloroethylene	VIII-28

LIST OF FIGURES

No.	Title	Page
III-1	Metabolic Pathways Involved in Oxidation of 1,1-Dichloroethylene by Cytochrome P-450 ..	III-13
III-2	Oxidation of 1,1-Dichloroethylene and Conjugation with Glutathione (GSH)	III-15
III-3	Two Compartment Pharmacokinetic Model for Dichloroethylenes Between a Closed Atmosphere and Animal and Metabolism	III-29
III-4	Three Compartment Pharmacokinetic Model for Describing Uptake of Dichloroethylenes by Rats	III-32

LIST OF ABBREVIATIONS

AFC	Antibody-forming cells
BUN	Blood urea nitrogen
bw	Body weight
^{14}C	Radioactive carbon
CCl_4	Carbon tetrachloride
CNS	Central nervous system
1,1-DCE	1,1-Dichloroethylene
cis-1,2-DCE	cis-1,2-Dichloroethylene
trans-1,2-DCE	trans-1,2-Dichloroethylene
1,2-DCEthane	1,2-Dichloroethane
DDT	Dichlorodiphenyltrichloroethane
DMN	Dimethylnitrosamine
DNA	Deoxyribonucleic acid
DWEL	Drinking Water Equivalent Level
GSH	Glutathione
HA	Health Advisory
IARC	International Agency for Research on Cancer
ip	Intraperitoneal
iv	Intravenous
Ke_q	Equilibrium constant
Km	Atmospheric concentration that causes *in vivo* metabolism to proceed at one-half maximal velocity
l	Liter
LC_{50}	Concentration lethal to 50% of recipients
LDH	Lactic dehydrogenase
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest Observed Adverse Effect Level
LT_{50}	Time necessary to kill 50% of recipients
MAO	Monoamine oxidase
MCL	Maximum contaminant level
MCLG	Maximum contaminant level goal
MFO	Mixed function oxidase
mg eq	Milligram equivalent
mm	Millimeter
ND	Not detected
NOAEL	No Observed Adverse Effect Level
NMR	Nuclear magnetic resonance
NTP	National Toxicology Program
PMA	Phorbol myristate acetate
po	Per os
ppm	Parts per million
PVDC	Polyvinylidene chloride copolymers
RBC	Red blood cells
RfD	Reference dose
S	Mixed partition coefficient
S-9	Liver homogenate
SAP	Serum alkaline phosphatase
SDH	Sorbitol dehydrogenase
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase

LIST OF ABBREVIATIONS (Continued)

SH	Sulfhydryl
SKF 525A	β-Diethylaminoethyl-2,2-diphenylpentanoate
SP	Point of saturation
Suc DH	Succinic dehydrogenase
TCA	Trichloroacetic acid
ug eg	Microgram equivalent
V_{max}	Maximum initial velocity of reaction at saturating concentration of substrate

I. SUMMARY

1,1-Dichloroethylene (1,1-DCE) is used industrially as a chemical intermediate in the manufacture of polyvinylidene chloride copolymers (PVDCs). The impermeability of these copolymers makes them useful as barrier coatings and they are widely used in the packaging industry as food wrappings. PVDCs also are used in the manufacture of nonflammable synthetic fibers and are extensively used as interior coatings for tanks, pipes, etc. The cis- and trans-1,2-DCEs have had limited use as solvents.

The DCEs, like other chlorinated hydrocarbons, cause depression of the central nervous system (CNS). Therefore, exposure to high concentrations of DCEs would cause narcosis and presumably could ultimately cause death due to respiratory depression.

Data on the toxic effects of cis- and trans-1,2-DCE are scant. However, 1,1-DCE has been shown to cause liver and kidney injury in animal studies and similar injuries would be expected after prolonged human exposures to high concentrations of the 1,2-DCEs.

Neither 1,1-DCE nor cis- or trans-1,2-DCE have been shown to be mutagenic without microsomal activation. However, with microsomal activation, 1,1-DCE was found to be mutagenic in bacterial systems, but not in V79 Chinese hamster cells or in dominant lethal studies in mice and rats. On the basis of the available data, IARC (1983) concluded that there is sufficient evidence to state that 1,1-DCE is mutagenic.

In one study, 1,1-DCE has been reported to produce kidney adenocarcinomas in male Swiss mice and mammary adenocarcinomas in Swiss mice and Sprague-Dawley rats. In addition, 1,1-DCE was shown to be an initiator in the skin papilloma test system in Swiss mice when given with phorbol myristate acetate. However, several other studies reported no evidence of carcinogenic potential in various strains of mice, rats and hamsters after inhalation or oral exposure.

In 1979, IARC stated that the available evidence indicated that 1,1-DCE caused malignant tumors in mice and rats and that some of the tumors were similar to those caused by vinyl chloride. IARC reevaluated the Maltoni data along with those from the NTP gavage bioassay and the Dow study. IARC's assessment of the available human data stated that these data were not adequate to permit assessment of 1,1-DCE's carcinogenic potential in humans (IARC, 1983). Although the final Maltoni study has been published (Maltoni, et al., 1985), the conflicting data from the various studies have prevented a definitive answer on the possible carcinogenicity of 1,1-DCE.

EPA recently finalized guidelines for the assessment of carcinogenic risk (U.S. EPA, 1986b). Applying these guidelines, the Office of Drinking Water determined, in a preliminary assessment, that the available data on the carcinogenic and mutagenic potentials of 1,1-DCE directs the characterization of its carcinogenic potential into Group C: Possible Human Carcinogen. There are no data for evaluating the carcinogenic potential of cis- or trans-1,2-DCE.

II. GENERAL INFORMATION AND PROPERTIES

A. Physical and Chemical Properties

The dichlorethylenes (DCEs) consist of three isomers; 1,1-DCE, cis- and trans-1,2-DCE. All are clear, colorless liquids with the molecular formula $C_2H_2Cl_2$ and a molecular weight of 96.95 (Windholz et al., 1976; Hardie, 1964).

1,1-Dichloroethylene. The 1,1-dichloroethylene isomer (also referred to as 1,1-DCE, vinylidene chloride, VDC and 1,1-dichloroethene) dissolves in organic solvents and is soluble in water to 400 mg/l at 20°C (Irish, 1963). Other estimates of 1,1-DCE's solubility in water range from 0.01 wt% (10 mg/l) to 0.64 wt% (640 mg/l) at temperatures varying from 4 to 25°C (Hardie, 1964; Ley et al., 1967; Wessling and Edwards, 1971; Jaeger and Stringer, 1972). More recently, DeLassus and Schmidt (1981) determined that the solubility of 1,1-DCE was nearly constant at 0.25 wt% (250 mg/l) over the range of 15 to 90°C. For air concentrations, one ppm is equivalent to 3.97 mg/m^3, and one mg/l is equivalent to 252 ppm, when measured at 25°C and 760 mm Hg (Irish, 1963). It is extremely volatile, having a vapor pressure of 591 Torr (mm Hg) at 20°C and boiling point of 31.5°C. It has a melting point of -122.1°C and a mild, sweet odor similar to that of chloroform. The liquid is heavier than air and will, therefore, settle in low places. It is also flammable, with 7.3 to 16.0% explosive limits in air at 28°C. The monomer polymerizes to a plastic at temperatures above 0°C, especially in the presence of oxygen or other catalysts.

vapor pressure of 265 Torr (mm Hg) at 20°C and a boiling point of 47°C. The vapor densities are identical to that of 1,1-DCE, which is over three times that of air (Windholz et al., 1976; Irish, 1963; Hardie, 1964; Lange and Forker, 1961). 1,2-DCEs are gradually decomposed by air, light and moisture, forming hydrogen chloride (HCl). The trans- form is noticeably subject to air oxidation (Windholz et al., 1976).

The 1,2-DCEs form azeotropes with water. This factor must be evaluated if evaporative purification of these isomers from water is considered. Horsely (1947) lists a binary azeotrope for cis-1,2-DCE with water (3.35% water by weight, boiling at 55.3°C) and a ternary azeotrope of this substance with water and ethanol (2.85% water, 90.5% cis-1,2-DCE and 6.65% ethanol by weight, boiling at 53.8°C). Azeotropes with ethanol or methanol also are formed.

Horsely (1947) similarly lists a binary azeotrope for trans-1,2-DCE with water (1.9% water by weight, boiling at 45.3°C) and a ternary azeotrope with water and ethanol (1.1% water, 94.5% trans-1,2-DCE and 4.4% ethanol by weight). The trans- isomer, like the cis-isomer, also forms an azeotrope with ethanol alone.

B. Manufacturing and Uses

1,1-Dichloroethylene. Mid-1970's annual production of 1,1-DCE approximated 120,000 metric tons (U.S. EPA, 1976). It is used primarily in the production of polyvinylidene chloride polymers and copolymers (PVDCs) and as a chemical intermediate in the synthesis of methylchloroform. Other monomers used with 1,1-DCE in copolymer production are vinyl chloride, acrylonitrile, and alkyl acrylates. The impermeability of PVDCs make them useful as barrier coatings on paper products and plastic films in the food packaging industry. [FDA regulations require that for the chloroform-soluble extractives of PVDC copolymer coatings on polyolefin, nylon and polycarbonate films contacting food may not exceed 0.5 mg/in^2, as extracted under conditions specific to the application (CFR, 1981). No such regulations were found for pure PVDC]. They are likewise used as binders for nonwoven fabrics, paint and concrete. 1,1-DCE polymers have been used extensively as interior coatings for ship tanks, railroad cars, and fuel storage tanks and for coating of steel pipes and structures (Wessling and Edwards, 1970; Hardie, 1964). The literature provides no quantitative information as to the concentration of the monomer, although this would be expected to be quite low following processing of the basic resin (e.g., coating, film, formation, storage).

1,2-Dichloroethylenes. 1,2-DCEs (singly or as a mixture) are used as a solvent for such substances as rubber, fats, phenol and camphor and for retarding fermentation. They are also used as a low temperature extraction solvent for heat sensitive substances and have been employed as a coolant in refrigeration plants (Windholz et al., 1976; Hardie, 1964). No production figures have been found, although Irish (1963) indicated that neither isomer has had wide industrial usage.

C. Extent and Significance of Problem

1,1-Dichloroethylene. Annual emissions of 1,1-DCE were estimated in 1975 to be 1.3 million lb/year, primarily from monomer production process vents and spills and from polymer production and processing. It is expected to be short-lived in water because of its limited water solubility and rapid volatilization to the atmosphere (Hushon and Kornreich, 1976). 1,1-DCE's tendency to form peroxides spontaneously in the presence of air or oxygen (Barr and Watts, 1972; Wessling and Edwards, 1970) would also be expected to limit its persistence in the atmosphere.

However, Pearson and McConnell (1975) indicate that degradation of such compounds dissolved in water is much slower that in the atmosphere. They estimate a tropospheric half-life of 8 weeks. In air, 1,1-DCE decomposed to carbon monoxide, carbon dioxide and hydrogen chloride when irradiated at wavelengths of light simulating atmosphere exposure. Therefore, those compounds may be the primary degradation products of 1,1-DCE in the natural atmosphere as well. The results of a sampling/analysis-method study of the air around or near industrial/waste disposal areas of the U.S. has been reported (Pellizzari, 1978). In general, the concentrations of 1,1-DCE in the air were low (typically <1 ug/m^3). Concentrations in drinking water, detected in water supplies of 4 out of 10 cities in the U.S., were also low (e.g., 0.1 ug/l) as shown in Table II-1 (U.S. EPA, 1975).

1,2-Dichloroethylenes. In view of their slow decomposition by air, light and moisture (Windholz et al., 1976), the 1,2-DCEs would be expected to be removed slowly from the environment. The tropospheric half-lives of the isomers are likely to be the same order of magnitude as estimated by Pearson and McConnell (1975) for 1,1-DCE (8 weeks). 1,2-DCEs have been detected in a limited number of U.S. drinking water supplies, as shown in Table II-1 (U.S. EPA, 1975).

Table II-1

Summary of Dichloroethylene Concentrations in Finished Drinking Waters at Ten Areas of the United States[a]

Area	Concentration, ug/l		
	1,1-Dichloroethylene	cis-1,2-Dichloroethylene	trans-1,2-Dichloroethylene
Miami, FL	D[b], 0.1	D[b], 16.0	D[b], 1.0
Seattle, WA	ND[c]	ND	ND
Ottumwa, IA	ND	ND	ND
Philadelphia, PA	D[b], 0.1	D[b], 0.1	ND
Cincinnati, OH	D[b]	D[b], 0.1	ND
Tucson, AR	ND	ND	ND
New York, NY	ND	ND	ND
Lawrence, MA	D[b]	ND	ND
Grand Forks, ND	ND	ND	ND
Terrebonne Parish, LA	ND	ND	ND

[a] From U.S.EPA, 1975, Table I-3.
[b] Detected by 500 ml volatile organic analysis, but not quantified.
[c] Not detected.

III. KINETICS

A. Absorption

Dichloroethylenes are neutral, low molecular weight, lipid soluble materials which should be readily absorbed following any route of administration.

Kinetic studies based on urinary, biliary and fecal excretion data have shown that administration of a single oral dose of 1,1-DCE in the dose range 0.5 to 50 mg/kg results in rapid and complete absorption (Jones and Hathway, 1978a; McKenna et al., 1978b; Reichert et al., 1979). Rapid absorption and distribution of 1,1-DCE after iv or ip administration have also been demonstrated (Jones and Hathway, 1978a).

It is well established that the absorption of gases from the lung is highly dependent on the blood:gas partition coefficient. As shown in Table III-1, the DCEs probably have a blood:gas partition coefficient in the range of 5 to 10, indicating that the materials equilibrate similar to a soluble vapor. In inspired air, these chemicals have been shown to come to a steady-state with the whole animal within 1 to 2 hr (Table III-1). The rate constant for reaching equilibrium has been determined to be 2.2 hr^{-1} (Andersen et al., 1979b). The blood:gas solubility of these compounds combined with the observation that they have a relatively short equilibration time suggests that they do not concentrate in poorly perfused tissues. Using relatively new kinetic procedures, a mixed partition coefficient (S), which is defined as the concentration of the chemical in the richly

Table III-1

Correlation of Physical and Chemical Characteristics to Inhalation Absorption and Distribution of Dichloroethylenes

	Blood:gas Partition Coefficient	Whole Body Equilibration Time	Mixed Partition Coefficient	Equilibration Constant	Boiling Point
		hr	S	K_{eq}	°C
cis-1,2-DCE	9.2[a]	2[b]	-	20[b]	60
trans-1,2-DCE	5.8[a]	1.5[b]	10.9[c]	11.5[b]	47
1,1-DCE	-	1[b,c]	4.0[c]	7.8[b]	31.5

[a] Sato and Nakajima, 1979. Data determined in experiments using human blood.

[b] Filser and Bolt, 1979. Data determined in experiments using rats.

[c] Andersen et al., 1980a. Data determined in experiments using rats.

perfused tissues divided by its concentration in the gas phase, has been determined for these chemicals (Andersen et al., 1980a). Rats exposed to trans-1,2-DCE have been shown by this method to absorb more chemical at equilibrium than rats exposed to 1,1-DCE (Table III-1). A similar kinetic analysis of the distribution of these chemicals has been performed (Filser and Bolt, 1979). They determined the equilibration constant (K_{eq}), which is defined as the clearance of a chemical from the chamber into the animal relative to clearance from the animal into the chamber, for all three chemicals. The data for K_{eq} show that, at equilibrium, the amount of chemical present in animals exposed to the DCEs would be cis-1,2-DCE > trans-1,2-DCE > 1,1-DCE. This study found an empirical relationship between K_{eq} and the volatility of the toxicant for a wide variety of halogenated ethylenes. Using the boiling point as a measure of volatility, it was shown that compounds with low boiling points have lower concentrations in tissue than those of higher boiling points. Thus, 1,1-DCE which has the lowest boiling point, would be expected to show the lowest concentration in tissue, while cis-1,2-DCE, which has the highest boiling point, would be expected to have the highest concentration in tissues (Table III-1).

Dallas et al. (1983) measured 1,1-DCE concentrations in blood samples from the femoral veins of anesthetized male Sprague-Dawley rats inhaling 25, 75, 150, or 300 ppm of 1,1-DCE. Absorption was very rapid and increased blood concentrations (about 25% of steady state) were present by 2 min. Equilibrium levels were reached by approximately 30 min for the three lower doses, while in animals exposed to the 300 ppm concentration, the blood levels tended to increase gradually over 3 hr.

B. Tissue Distribution

Studies with 1,1-DCE have been performed using both fed and fasted animals because 1,1-DCE is known to be more hepatotoxic in fasted animals (Jaeger et al., 1974). The distribution of 1,1-DCE to various organs of rats following inhalation exposure for 2 hr at an initial concentration of 2000 ppm has been studied using [^{14}C]1,1-DCE (Jaeger et al., 1977a). The concentration of total radioactivity 30 min after cessation of exposure was highest in the blood followed by kidney, liver, spleen, heart and brain in both the fed and fasted rats. The distribution of trichloroacetic acid (TCA) insoluble labeled material, hereafter referred to as covalently bound material, followed a similar pattern with the following exception. While the kidney contained very little covalently bound ^{14}C, approximately one-third of the ^{14}C in the liver was covalently bound (Jaeger et al., 1977a).

Similar studies have been conducted on rats 72 hr after inhalation exposure to either 10 or 200 ppm [^{14}C]1,1-DCE for 6 hr (McKenna et al., 1977, 1978a), and the tissue distribution data of ^{14}C are given in Table III-2. At either exposure level, the highest concentrations of ^{14}C were found in the liver and kidney. When tissue concentration data were normalized to account for differences in end-exposure body burdens, the greatest percentages of the body burden per gram of tissue

Table III-2

Relative Amounts of ^{14}C in Tissues 72 Hours After Exposure to 10 or 200 ppm [^{14}C]1,1-DCE for 6 Hours

Microgram Equivalents of [^{14}C]1,1-DCE per gram of Tissue

	10 ppm		200 ppm	
Tissue	Fed Rats	Fasted Rats	Fed Rats	Fasted Rats
Liver	0.56 (0.075)	0.57 (0.097)[a]	15.75 (0.147)	19.57 (0.204)[a]
Kidney	1.68 (0.228)	1.85 (0.314)[a]	3.15 (0.079)	19.90 (0.208)[a]
Lung	0.19 (0.026)	0.21 (0.036)[a]	5.19 (0.044)	7.12 (0.074)[a]
Fat	0.07	0.06	0.74	1.25
Muscle	0.06	0.04	0.91	1.19
Skin	0.19	0.15	3.78	5.98
Carcass	0.08	0.06	1.68	2.18
Plasma	0.15	0.16	3.15	5.20[a]

( ) Represent tissue burdens normalized for differences in end-exposure body burden of ^{14}C activity. Microgram equivalents of [^{14}C]1,1-DCE per gram of tissue/total milligram equivalents recovered per rat.

[a] Significantly different from fed rats of the same exposure group, $P < 0.05$, Student's *t* test.

Based on McKenna et al., 1978a.

were found in the kidney, liver and lung and were consistently higher in fasted rats. Only a small amount of the ^{14}C was found in the fat. Table III-3 compares the extent of covalent binding of ^{14}C and the total biotransformation of 1,1-DCE. A comparison of fed and fasted rats at the different exposure concentrations shows that the concentration of covalently bound ^{14}C in the liver is higher in fasted rats. Although fasted rats metabolize less 1,1-DCE than fed rats, the concentration of covalently bound ^{14}C activity in the liver was greater in fasted than fed rats following exposure to 200 ppm. The increase in covalent binding in the livers of fasted rats was more apparent after normalization of the data to account for differences in the biotransformation of 1,1-DCE (B/A ratio, Table III-3).

Distribution to the organs of rats following intragastric administration of 25 mg/kg bw of [^{14}C]1,1-DCE also has been studied (Jones and Hathway, 1978a). Sequential autoradiograms of longitudinal sagittal sections through whole animals showed high ^{14}C concentrations in the kidneys and liver after 30 min and a more general distribution of ^{14}C throughout the soft organs of the body at 1 hr. The kidneys and liver retained ^{14}C for the longest time after dosing.

Distribution studies also have been conducted with rats 72 hr after administration of a single oral dose of 1 or 50 mg/kg [^{14}C]1,1-DCE (McKenna et al., 1978b). The distribution of ^{14}C to different tissues (Table III-4) was shown to be independent of dose and not to be influenced by fasting the

It also forms explosive peroxides in contact with air and is stored and shipped either with an inhibitor (e.g., 200 ppm hydroquinone monomethyl ether) or refrigerated under an inert gas atmosphere in the absence of light and air (Warren and Ricci, 1978; Windholz et al., 1976; Hardie, 1964). The octanol/water partition coefficient for 1,1-DCE was reported as 5.37 (log P = 0.73) by Radding et al. (1977), indicating that it should not accumulate significantly in aquatic animals (U.S. EPA, 1980).

None of the three azeotrope listings (the first of which is extensive) indicates that 1,1-DCE forms azeotropes with water (Horsely, 1947; Lange and Forker, 1961; Perry and Chilton, 1973), although it does form an azeotrope with methanol. Since azeotropes occur infrequently between compounds with boiling points differing by more than about 30°C (Perry and Chilton, 1973), an azeotrope between 1,1-DCE (31.5°C boiling point) and water (100°C) is unlikely to occur, eliminating this as a concern during possible evaporative purification of water from the chemical.

1,2-Dichloroethylenes. These isomers are sometimes referred to as acetylene dichloride, 1,2-dichloroethene, sym-dichloroethylene and dioform. The marketed product is generally a mixture of cis- and trans- isomers. Both the cis- and trans- isomers are somewhat soluble in water (3,500 mg/l and 6,300 mg/l at 25°C, respectively), but are readily soluble in most organic solvents. The volatilities of the 1,2-DCEs are less than that of 1,1-DCE. The cis- isomer has a vapor pressure of 180 Torr (mm Hg) at 20°C and boils at 60°C, while trans- isomer has a

Table III-3

Metabolism of [^{14}C]1,1-DCE and Covalent Binding of ^{14}C to Rat Hepatic Tissue After Inhalation Exposure to 10 or 200 ppm of [^{14}C]1,1-DCE

		A	B	B/A
Concentration and Pretreatment	Body Burden (mg of [^{14}C]1,1-DCE/kg	Metabolized [^{14}C]1,1-DCE (mgEq/kg)	Microgram Equivalents of [^{14}C]1,1-DCE bound per gram of liver protein	
10 ppm				
Fed	2.89	2.84	2.49	0.88
Fasted	2.30	2.26	2.47	1.10
200 ppm				
Fed	44.53	42.73	64.18	1.49
Fasted	35.93[a]	32.92[a]	79.46	2.42[a]

[a] Significantly different than fed rats exposed to the same concentration of 1,1-DCE, $P < 0.05$, Students test.

Based on McKenna et al., 1978a.

Table III-4

Relative Amount of ^{14}C in Tissues 72 Hours After a Single Oral Dose of 1 or 50 mg/kg of $[^{14}C]$1,1-DCE[a]

Tissue	1 mg/kg		50 mg/kg	
	Fed	Fasted	Fed	Fasted
Liver	0.063	0.101	0.089	0.073
Kidney	0.030	0.028	0.018	0.033
Lung	0.013	0.001	0.003	0.019
Fat	0.014	0.108	ND	ND
Muscle	0.007	0.005	ND	ND
Skin	0.018	0.014	0.009	0.015
Carcass	0.008	0.008	0.006	0.007
Whole Blood	0.013	0.011	0.013	0.016

[a] Expressed as percentage of dose per gram of tissue.
ND = Not detected.
Based on McKenna et al., 1978b.

animals. The greatest percentage of the ^{14}C dosage per gram of tissue 72 hr after administration was found in the liver. Table III-5 compares the extent of covalent binding of ^{14}C to hepatic tissue macromolecules with the amount of [^{14}C]1,1-DCE metabolized. There were no differences in covalent binding on a per gram protein basis in fed and fasted animals. However, normalization of the data to account for differences in metabolism (B/A, Table III-5) showed an increase ($P < 0.05$) in the amount of ^{14}C covalently bound to liver macromolecules in fasted rats at the 50 mg/kg level.

Subcellular distribution of [^{14}C] 30 min following inhalation of 2,000 ppm of [^{14}C]1,1-DCE for 2 hr was determined in the microsomal, mitochondrial and cytosolic compartments of the liver (Jaeger et al., 1977a). More ^{14}C was found in the liver fraction from fasted rats than from fed rats. Since its concentration was about the same in all three compartments of the liver, there was no marked subcellular localization of radiolabelled carbon. The ^{14}C in microsomes and mitochondria was largely covalently bound (TCA-insoluble), while the cytosol contained substantial amounts of TCA-soluble ^{14}C, suggesting the presence of metabolites. In addition, significant amounts of the ^{14}C in microsomes and mitochondria was $CHCl_3$-soluble, suggesting that there also was considerable binding of ^{14}C to lipids. The turnover rate of TCA-insoluble radioactivity derived from 1,1-DCE has a half-life of 2 to 3 hr.

There are no data on the distribution of the 1,2-DCE isomers.

Table III-5

Metabolism of $[^{14}C]$1,1-DCE and Covalent Binding of ^{14}C to Rat Hepatic Tissue 72 Hours After a Single Oral Dose of $[^{14}C]$1,1-DCE

	(A)	(B)	B/A
Pretreatment	Metabolized $[^{14}C]$1,1-DCE (mgEq/kg)	Covalently bound 1,1-DCE (ug Eq of $[^{14}C]$1,1-DCE/ gram liver protein	
1 mg/kg			
Fed	0.956	0.854	0.89
Fasted	0.924	0.861	0.93
50 mg/kg			
Fed	39.08	37.67	0.96
Fasted	31.86	44.45	1.40[a]

[a] Significant fed vs fasted difference, $P < 0.05$, Student's test.

Based on McKenna et al., 1978b.

C. Biotransformation

The comparative biotransformation of DCEs has been studied extensively. Metabolic end products of chlorinated ethylenes are predominantly alcohols and carboxylic acids. Perfusion of the isolated rat liver with a medium containing either cis-1,2-DCE or trans-1,2-DCE produced dichloroethanol and dichloroacetic acid (Bonse et al., 1975), suggesting the initial formation of dichloroacetaldehyde. In the liver, the ratio of biotransformation to uptake was much greater for the cis- isomer than for the trans- isomer.

Chloroacetic acid has been identified as a product in the biotransformation of 1,1-DCE in perfused rat liver. Inhibition of epoxide hydrase in *in vitro* studies using rat liver S-9 (liver homogenate) fraction resulted in a stimulation of chloroacetic acid formation from 1,1-DCE, leading to the conclusion that the glycol intermediate is relatively unimportant in the conversions of 1,1-DCE to chloroacetic acid (Leibman and Ortiz, 1977). Additionally, studies using competitive epoxide substrates have shown that epoxide hydrating pathways are of minimal significance in the formation of reactive intermediates of 1,1-DCE (Andersen et al., 1980b).

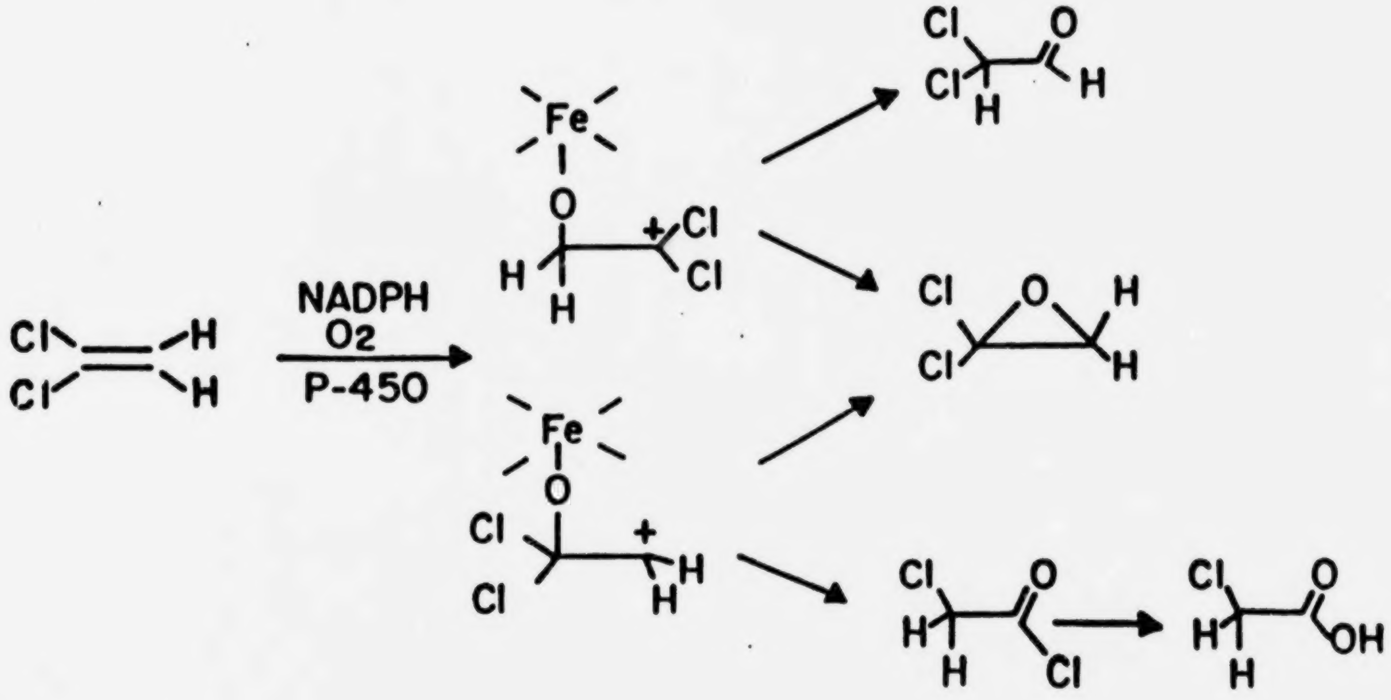
Although it had been speculated in early reports that the epoxide of 1,1-DCE (1,1-DCE oxide) was involved in the metabolism of 1,1-DEC, the compound had not been synthesized. Recently, Liebler and Guengerich (1983) made this epoxide and characterized it using NMR (^{13}C,^{1}H) and mass spectral techniques. It is highly unstable in water and decomposes to form a variety of products;

2-chloroacetic acid and glycolic acid are formed at very low pH; carbon monoxide, formaldehyde and formic acid are formed at neutral and basic pH. These compounds are inconsistent with the known metabolites of the microsomal oxidation of 1,1-DCE, which are chloroacetic acid and dichloroacetaldehyde (Liebler and Guengerich, 1983). Dichloroacetaldehyde was not formed under these conditions or when the 1,1-DCE oxide was added in stoichiometric amounts to purified cytochrome P-450. While it was possible to form dichloroacetaldehyde from 1,1-DCE oxide in organic solvents in the presence of very high concentrations of ferric bromide, complexation of the iron into a model porphyrin to model the enzyme abolished its ability to cause this rearrangement. The ratio of the products, 2,2-dichloroacetaldehyde and chloroacetic acid (and suicide inactivation of cytochrome P-450) varied among a number of different cytochrome P-450 isozymes, in spite of the view that an epoxide intermediate formed all of the metabolites. Low levels of the epoxide were trapped in microsomal reactions with a nucleophile; however, the levels of epoxide formed were at least an order of magnitude too low to support the obligate intermediary of an epoxide in the formation of the other products of 1,1-DCE biotransformation.

A scheme for the biotransformation of 1,1-DCE based on the work of Liebler and Guengerich (1983) is shown in Figure III-1. The formal chloride shift has precedent in previous work with 1,1,2-trichloroethylene (Miller and Guengerich, 1982), where evidence against the role of an epoxide in the formation of chloral (2,2,2-trichloroacetaldehyde) requires a formal hydride

Figure III-1

Metabolic Pathways Involved in Oxidation of 1,1-Dichloroethylene by Cytochrome P-450


NADPH
O2
P-450
Fe
O
Cl
H
OH
+

Adapted from Liebler and Guengerich, 1983.

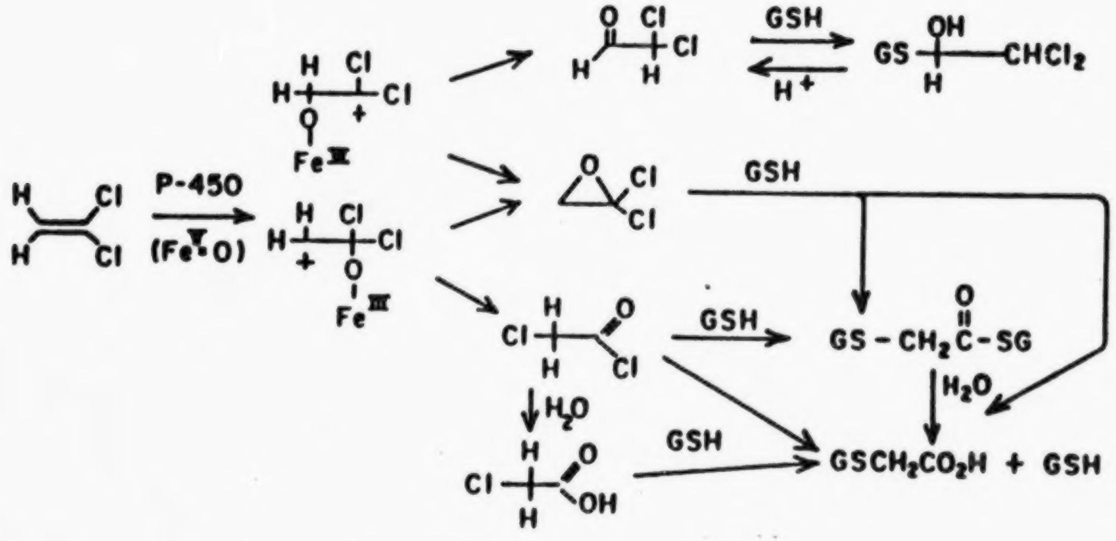
shift. Deuterium studies showed that such a shift did occur (Liebler and Guengerich, 1983). The occurrence of such hydride shifts without epoxides in non-halogen systems involving cytochrome P-450 and other oxidations has now been demonstrated (Groves and Myers, 1983; Liebler and Guengerich, 1983; Mansuy et al., 1984).

Other recent studies have examined the nature of the primary glutathione (GSH) conjugates formed during metabolism of 1,1-DCE. Rat liver microsomal incubations fortified with NADPH and GSH formed three GSH conjugates identified as S-(2,2-dichloro-1-hydroxy)ethyl-GSH, S-(2-glutathionyl)-acetyl-GSH and S-carboxymethyl-GSH (Figure III-2). The first adduct results from the reaction of 2,2-dichloroacetaldehyde with GSH. However, this adduct was not found in isolated hepatocytes, presumably because it is oxidized and reduced more rapidly than it is conjugated (Liebler et al., 1984). Thus, this adduct may not be formed *in vivo*. The second adduct, S-(2-glutathionyl)acetyl-GSH, is partially stable (half-life = 4 hr at neutral pH in buffer) and probably corresponds to the unknown acetyl derivatives postulated by Jones and Hathway (1978a). The compound hydrolyzes to form S-carboxymethyl-GSH which can be transformed further to yield thiodiglycolic acid, N-acetyl-S-(2-hydroxyethyl)cysteine and N-acetyl-S-(2-carboxymethyl)-cysteine (Jones and Hathway, 1978a; McKenna et al., 1978a; Reichert et al., 1979).

The identity of the primary 1,1-DCE metabolite which reacts with GSH has not been unambiguously proven. However,

Figure III-2

Oxidation of 1,1-Dichloroethylene and Conjugation with Glutathione (GSH)


P-450
(Fe^V=O)
Fe^III
GSH
H+
GS-CHOH-CHCl2
GSH
GSH
H2O
GS-CH2C(=O)-SG
H2O
GSH
GSCH2CO2H + GSH

Adapted from Liebler _et al_., 1984.

kinetic studies with GSH and a model thiol indicated that 2-chloroacetyl chloride reacted at least one thousand times faster than the 1,1-DCE oxide, 2,2-dichloroacetaldehyde or 2-chloroacetic acid (Liebler et al., 1984). These studies, coupled with evidence for only low level transformation of the epoxide to 2-chloroacetyl chloride at pH greater than 2 (Liebler and Guengerich, 1983), would suggest that the most prominent aspect of the biotransformation of 1,1-DCE is the transfer of chloride ion in the cytochrome P-450 intermediate to form 2-chloroacetyl chloride and the subsequent reaction of that species with GSH or protein.

In live animals, it has been established that 1,1-DCE metabolites are conjugated with GSH, presumably a detoxication process (McKenna et al., 1977, 1978a,b; Jones and Hathway, 1978a; Reichert et al., 1978, 1979). The major urinary metabolites have been determined in several studies. McKenna et al., (1978a,b) have isolated four main metabolites in rat urine, two of which they have identified: thiodiglycolic acid and the mercapturic acid N-acetyl-S-(2-hydroxyethyl) cysteine which was present in the highest amount. Both of these materials presumably would be formed as a result of conjugation of one of the metabolites with GSH. Jones and Hathway (1978a) have found two major metabolites in rat urine: thiodiglycolic acid and a postulated N-acetyl-S-cysteinyl-acetyl derivative. In addition, they have shown that chloroacetic acid, dithioglycolic acid and thioglycolic acid were present in lesser concentrations. The formation of the N-acetyl-S-cysteinyl-acetyl derivative was unexpected, since this material was not produced in the biotransformation of chloroacetic acid administered in rats. This suggested that the N-acetyl-S-cysteinyl-acetyl derivative was derived from a metabolite prior to the formation of chloroacetic acid, perhaps the 1,1-DCE oxide or chloroacetyl chloride, which was conjugated with GSH. Reichert et al. (1979) identified three metabolites in rat urine: thioglycolic acid, the major metabolite, N-acetyl-S-(2-carboxymethyl)cysteine and methylthioacetylaminoethanol. In addition, three unidentified compounds were present in lesser concentrations. The identification of methylthioacetylaminoethanol suggests that, in addition to GSH conjugation, a totally different reaction mechanism must exist which leads to the formation of ethanolamine derivatives. The ethanolamine is postulated to originate from membrane lipids which react with 1,1-DCE epoxide or other metabolites.

In the intact rat, several studies have shown that a large portion of absorbed 1,1-DCE is metabolized (Table III-6). The fifth column shows the percent of the dose excreted into the air as CO_2 and is a reflection of metabolism. Thus, as the dosage is increased, a larger absolute amount of metabolites is formed, but a smaller percentage of the dose is metabolized. This results from the fact that when the biotransformation processes are saturated, more of the parent compound is excreted into the air. This was observed after oral, ip or inhalatory administration. In addition, fasting also influenced the biotransformation. Fasted rats had lower body burdens at the end of the experiments and biotransformed less than did fed rats.

Table III-6

Metabolism and Disposition of [^{14}C] 1,1-Dichloroethylene in Rats

		Time	% of Original Dose of [^{14}C] Activity					
Dose mg/kg	Route	After Dose	Pulmonary 1,1-DCE	Excretion CO_2	Renal Excretion	Biliary Excretion	Residual in Body	References
0.5	oral	72	1.26	13.64	43.55	15.74	5.57	Reichert et al., 1979
5	oral	72	9.70	11.35	53.88	14.54	2.83	
50	oral	72	16.47	6.13	42.11	7.65	2.77	
0.5	oral	72	0.9	23	52		2-4	Reichert et al., 1978
50	oral	72	20	6	36			
0.5	oral	0-24	0.6	3.9	71.3	5.1		Jones and Hathway, 1978a
		24-48	0.06	0.5	5.3	2.7		
		48-72	0.08	0.5	3.6	0.6		
		Total	0.07	4.8	80.2	8.3		
0.5	iv	0-24	80.0	3.5	14.4	0.3		Jones and Hathway, 1978a
		24-48	0	0	0.7	0.1		
		48-72	0	0	0	0		
		Total	80.0	3.5	15.0	0.4		
0.5	ip	0-24	11.4	2.6	65.8	14.2		Jones and Hathway, 1978a
		24-48	0.2	0.5	2.0	1.6		
		48-72	0.1	0.5	1.2	0.4		
		Total	11.7	3.6	69.0	16.2		
350	oral	0-24	62.4	0.3	17.6	0.4		Jones and Hathway, 1978a
		24-48	4.8	0.4	10.0	0.5		
		48-72	0.1	0.3	1.9	0.4		
		Total	67.3	1.0	29.5	1.3		
350	ip	0-24	90.5	0.7	7.1	0.5		Jones and Hathway, 1978a
		24-48	0.6	0.5	0.3	0.1		
		48-72	0	0.1	0.3	0.1		
		Total	91.1	1.3	7.7	0.7		
1	oral[a]	72	2.89	10.85	62.68	16.25	3.18	McKenna et al., 1978b
1	oral[b]	72	1.36	7.82	66.42	11.18	3.46	
50	oral[a]	72	18.75	4.16	46.62	4.14	2.39	
50	oral[b]	72	29.23	3.19	34.88	4.28	3.08	

(continued next page)

Table III-6 (Continued)

Dose mg/kg	Route	Time After Dose	% of Original Dose of [^{14}C] Activity: Pulmonary 1,1-DCE	Excretion CO_2	Renal Excretion	Biliary Excretion	Residual in Body	References
2.89[c]	inhal[a]	72	1.63	8.74	74.72	9.73	4.75	McKenna et al., 1977, 1978a
2.30[d]	inhal[b]	72	1.60	8.27	78.19	6.75	5.28	
44.53[c]	inhal[a]	72	4.17	8.22	74.66	6.39	6.18	
35.39[d]	inhal[b]	72	8.36	7.24	70.41	2.72	10.52	
[e]	inhal[a]	24			36.7			Jaeger et al., 1977a
[e]	inhal[b]	24			36.5			

[a] Fed rats.

[b] Fasted rats.

[c] Total body burden after 6 hr exposure to 10 ppm.

[d] Total body burden after 6 hr exposure to 200 ppm.

[e] Exposure for 2 hours to gas with initial concentration of 2000 ppm.

Studies comparing the relative ability of mice and rats to biotransform 1,1-DCE have been conducted. Disposition of ^{14}C from [^{14}C]1,1-DCE in mice and rats is shown in Table III-7 (McKenna et al., 1977b). These data show that, at identical exposure levels (10 ppm), the mouse develops a higher body burden of 1,1-DCE and/or metabolites than the rat, but the disposition of 1,1-DCE in both species appears to be quite similar. However, as a result of a more rapid metabolic rate, covalently bound metabolites of 1,1-DCE are higher in the mouse than in the rat (Table III-8). This increasd biotransformation in the mouse has been postulated to be responsible for the increased sensitivity of the mouse to the potential carcinogenic and toxic effects of 1,1-DCE (Hathway, 1977).

When the same oral dose (50 mg/kg) of 1,1-DCE was administered, mice metabolized a greater proportion (Jones and Hathway, 1978b) than did rats. Mice formed considerably more of the N-acetyl-S-cysteinyl-acetyl derivative, and excreted a small amount of N-acetyl-S-(2-carboxy-methyl)-cysteine, which was not found in rat urine. The efficiency of DCE biotransformation appeared to parallel the relative activity of the cytochrome P-450 systems in the animal livers and it was suggested that "real exposure," expressed as the amount biotransformed, is higher for orally dosed mice than rats (Table III-9).

Studies of the effects of various inducers and inhibitors of microsomal enzymes on the rate of 1,1-DCE biotransformation have been conducted using isolated perfused livers (Reichert and Henschler, 1978; Reichert et al., 1978) and whole animals

Table III-7

Disposition of [^{14}C] Following Inhalation of 10 ppm 1,1-DCE Over a 48 Hour Period

	Mice	Rats
Expired 1,1-DCE %	0.65 ± 0.07	1.63 ± 0.14
Expired $^{14}CO_2$ %	4.64 ± 0.17	8.74 ± 3.72
Body Burden %		
Urine	80.83 ± 1.68	74.72 ± 2.30
Feces	6.58 ± 0.81	9.73 ± 0.10
Carcass	5.46 ± 0.41	4.75 ± 0.78
Cage Wash	1.83 ± 0.84	0.44 ± 0.28
Body Burden mg eq[a]		
1,1-DCE/kg	5.30 ± 0.75	2.89 ± 0.24
Total Metabolized		
mg eq[a] 1,1-DCE/kg	5.27 ± 0.74	2.84 ± 0.26

[a] mg eq -- milligram equivalents.

Based on McKenna et al., 1977b.

Table III-8

Covalently Bound ^{14}C in Rat and Mouse following Exposure to 10 ppm $[^{14}C]$-1,1-DCE

	^{14}C-1,1-DCE, ug eq[a]/mg Protein	
	Liver	Kidney
Mice	22.29 ± 3.77	79.55 ± 19.11
Rats	5.28 ± 0.14	13.14 ± 1.15

[a] ug eq -- microgram equivalents

Based on McKenna et al., 1977b

Table III-9

Relative Proportion of $[^{14}C]$ Excretory Products After Oral Administration of 50 mg/kg of $[^{14}C]$1,1-DCE to Rodents

	^{14}C Expressed as % of Dose	
$[^{14}C]$ Excretory Products	Mice	Rats
Unchanged DCE via pulmonary route	6	28
CO_2 excretion	3	3.5
Chloroacetic acid	0	1
Thiodiglycolic acid	3	22
Thioglycolic acid	5	3
Dithioglycolic acid	23	5
Thioglycolyloxalic acid	3	2
N-acetyl-S-cysteinyl acetyl derivative	50	28
N-acetyl-S-(2-carboxymethyl) cysteine	4	0
Urea	3	3.5

Based on Jones and Hathway, 1978b.

(Andersen et al., 1979b) (Table III-10). These studies give disparate results for the effects of phenobarbital and SKF 525A, but these may be due to the differences in experimental technique, i.e., whole animal compared to isolated perfused liver.

Exposure of rats to trans-1,2-DCE or cis-1,2-DCE was shown to cause exhalation of acetone (Filser et al., 1978). However, this acetone may not be a metabolite, but rather the result of a DCE-induced alteration in lipid and fatty acid metabolism.

Filser and Bolt (1980) studied this phenomenon further in adult male Wistar rats and concluded (based largely upon studies with the analog vinylidene fluoride) that the increased acetone expiration caused by inhalation of cis- or trans-1,2-DCE (110 to 135 ppm and 340 to 900 ppm, respectively) does not stem from the halocarbons themselves, but requires their biotransformation. This conclusion was based on the dependence of acetone production on vinylidene fluoride concentration, effects of agents which induce oxidative enzymes, effects of the metabolic inhibitor, pyrazole, effect of cysteine, effect of hypoxia and the time course of acetone exhalation. Furthermore, Filser et al. (1982) showed that increased acetone exhalation also could be produced by administration of fluoroacetate or chloroacetate, known metabolites of the dihaloethylenes. These haloacetates are effective inhibitors of the citric acid cycle and this is believed to be the underlying mechanism. However, the role of this process in the toxicity of the DCEs is uncertain.

Table III-10

Effects of Inducers and Inhibitors of Microsomal Enzymes on Rate of Metabolism of 1,1-DCE

Chemical	Experimental Method	Metabolism	Investigator
CCl_4	whole animal	decrease	a
Pyrazole	whole animal	decrease	a
Aminotriazole	whole animal	decrease	a
2,3-Epoxypropan-1-ol	whole animal	no effect	a
Phenobarbital	whole animal	no effect	a
Phenobarbital	isolated perfused liver	increase	b
SKF 525A	whole animal	no effect	a
SKF 525A	isolated perfused liver	decrease	b
DDT	isolated perfused liver	increase	b
Decreased glutathione	isolated perfused liver	decrease	b

[a] Andersen et al., 1979b.
[b] Reichert and Henschler, 1978, Reichert et al., 1978.

Using isolated rat liver microsomes, both cis- and trans-1,2-DCE have been shown to be competitive inhibitors of the mixed-function oxygenase (MFO) system (Freundt and Macholz, 1978).

Costa and Ivanetich (1982) have studied the biotransformation of both cis- and trans-1,2-DCE in rat liver microsomes supplemented with NADPH. 2,2-Dichloroethanol and 2,2-dichloroacetic acid were formed, presumably by reduction or oxidation formed of 2,2-dichloroacetaldehyde. Treatment of rats with either phenobarbital or β-naphthoflavone increased the formation of 2,2-dichloroacetaldehyde from either cis- or trans-1,2-DCE.

D. Excretion

Considerable work on the excretion of 1,1-DCE and its metabolites has been done using [^{14}C]1,1-DCE (Jaeger et al., 1977a; McKenna et al., 1977, 1978a,b; Jones and Hathway, 1978a; Reichert and Werner, 1978; Reichert et al., 1979). The data show that both unmetabolized 1,1-DCE and CO_2 formed by metabolism of 1,1-DCE are excreted via the lung, whereas the other metabolites are eliminated via urine and feces (Table III-6). However, the pattern of excretion depends upon the concentration of 1,1-DCE in the blood. The blood level is affected by the amount of chemical administered and by the route of administration. At low dose levels where the concentration of 1,1-DCE in the blood is low and biotransformation is effective, most of the ^{14}C is eliminated as metabolites via renal and fecal excretion. Some of the urinary metabolites were of biliary origin and entered the urine after enterohepatic circulation (Jones and Hathway, 1978a). At higher dose levels, the concentration of 1,1-DCE in blood is increased as biotransformation approaches saturation and the liver becomes less effective in removing the xenobiotic from the blood. As a result, more 1,1-DCE is eliminated through the lung as reflected by the relative amount of ^{14}C excreted as 1,1-DCE via the lung. Another example of the effect of biotransformation on elimination is seen by comparing the excretion following a low dose (0.5 mg/kg) of 1,1-DCE administered iv with excretion following oral or ip administration. Oral or ip administration presents 1,1-DCE to the liver for biotransformation while iv administration permits systemic distribution of 1,1-DCE and each pass brings approximately 25% of the blood to the liver. Accordingly, the excretion by the lung becomes more important following iv administration; a large part of the ^{14}C is eliminated as untransformed 1,1-DCE via the lung, rather than being eliminated as metabolites via the renal and fecal routes.

Since most of the total absorbed dose is eliminated in the first 24 to 72 hr after administration, the rate of elimination is relatively rapid (Jaeger et al., 1977a; McKenna et al., 1977, 1978a; Jones and Hathway, 1978a). Disappearance of covalently bound metabolites of 1,1-DCE also appears to be fairly rapid with a reported half-life of 2 to 3 hr (Jaeger et al., 1977a).

No data concerning the excretion of cis- and trans-1,2-DCE are available.

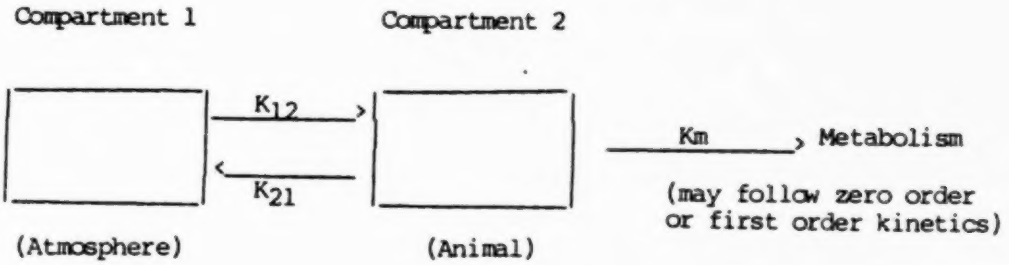
E. Kinetics

Several studies have shown that the kinetic behavior of the halogenated ethylenes is dose-dependent, evidently the result of saturability of the metabolic pathways of the organism at higher doses (Jones and Hathaway, 1978a; McKenna et al., 1978a, 1978b; Reichert and Henschler, 1978; Reichert and Werner, 1978; Andersen et al., 1979a,b, 1980a; Filser and Bolt, 1979). A hypothetical two compartment kinetic model (Figure III-3) has been employed to explain the results of inhalation studies of halogenated ethylenes (Filser and Bolt, 1979). In their closed system, saturation of the metabolic capacity was observed at high levels of exposure. When rats were exposed to atmospheric concentrations which exceeded the "point of saturation (SP)," biotransformation followed zero-order kinetics, i.e., the rate was independent of the concentration (Filser and Bolt, 1979). Concentrations below this level resulted in normal first-order kinetics, i.e., the rate of metabolism was dependent upon the concentration.

The first-order clearance of the three DCEs is shown in Table III-11. Cis-1,2-DCE has the highest rate of clearance, trans-1,2-DCE the lowest and 1,1-DCE intermediate. The concentration of the DCEs in the air at which there is a transition from first-order to zero-order biotransformation also is shown in Table III-11. The concentration necessary to saturate biotransformation was much higher for 1,1-DCE than for the 1,2-DCEs. Although the *in vivo* transformation of DCEs does not follow simple Michaelis-Menten kinetics, a zero-order

Figure III-3

Two Compartment Pharmacokinetic Model for DCEs Between a Closed Atmosphere and Animal and Metabolism


Compartment 1
Compartment 2
K_{12}
K_{21}
Km
Metabolism
(may follow zero order or first order kinetics)
(Atmosphere)
(Animal)

Based on Filser and Bolt, 1979.

Table III-11

First-Order and Zero-Order Metabolic Elimination of DCEs from a Closed Exposure System: Saturation Points (SP) and Metabolic Rates Expressed as V_{max} and Clearance, Based on 1 kg Body Weight

Chemical	First Order Clearance $\frac{\text{liter}}{\text{hr/kg body weight}}$	Saturation Point, SP (ppm in air)	hr/kg body weight
1,1-DCE	17	150	100
trans-1,2-DCE	11	(15)	7
cis-1,2-DCE	30	20	25

( ) Not observed experimentally, but obtained extrapolation, i.e., from intersection of observed zero-order and first-order declines.

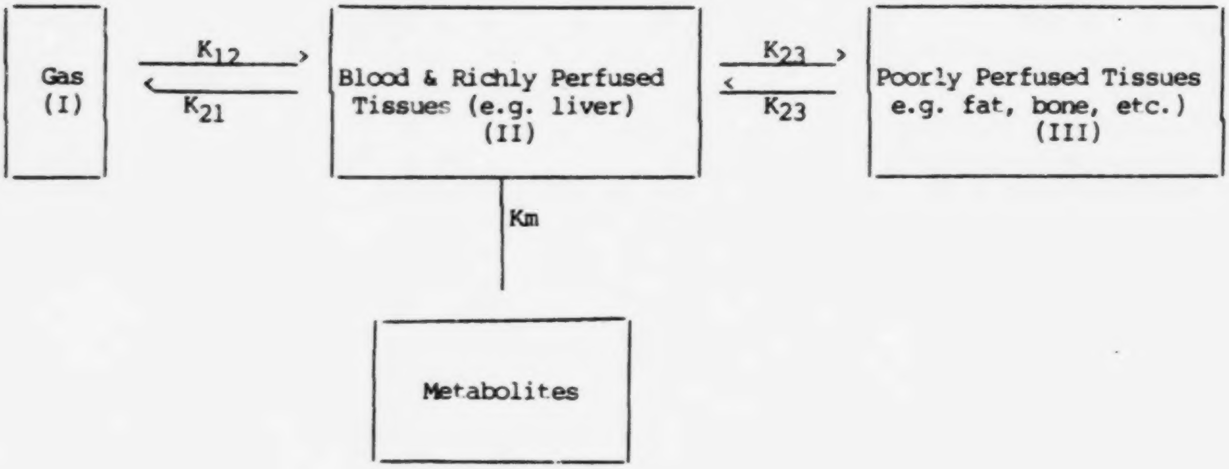
Filser and Bolt, 1979.

kinetic rate constant (V_{max}) for biotransformation under saturation conditions could be determined (Table III-11). This rate constant measures the maximum rate of biotransformation of a particular chemical. The V_{max} for 1,1-DCE is much higher than for the 1,2-DCEs. The V_{max} values are quite different for the isomeric DCEs even when a correction is made for the differing tissue concentrations of these materials. This suggests that the chemical structure affects the maximum velocity of biotransformation. For the DCEs, the relative rate of biotransformation was determined to be 1,1-DCE >> cis-1,2-DCE > trans-1,2-DCE (Table III-11).

A hypothetical three compartment, steady-state, kinetic model (Figure III-4) also has been used to explain kinetic data obtained in inhalation studies using gas uptake measurements (Andersen et al., 1979a,b; 1980a). According to this model, tissues richly perfused with blood rapidly equilibrate with the DCEs. Following the initial blood:gas equilibration, the blood concentration of DCEs is decreased by metabolism in the richly perfused tissues, storage in the poorly perfused tissues and excretion. Excretion of the unmetabolized volatile DCEs occurs primarily via the lungs. For both 1,1-DCE and the trans-1,2-DCE, there were significant contributions to the overall gas uptake rate from both a first-order process, k_{23}, representing storage in the poorly perfused tissues, and a saturable process, k_m, representing biotransformation. At very high concentrations, the relative contribution of the first-order process (storage in poorly perfused tissue) to the overall

Figure III-4

Three Compartment Pharmacokinetic Model for Describing Uptake of DCEs by Rats


Gas
(I)
K_{12}
K_{21}
Blood & Richly Perfused Tissues (e.g. liver)
(II)
K_{23}
K_{23}
Poorly Perfused Tissues e.g. fat, bone, etc.)
(III)
Km
Metabolites

Based on Andersen et al., 1980a.

gas uptake rate was increased. At lower concentrations, the first-order process became less important and the saturable metabolic process became the main route of gas uptake by the animal. The concentration dependence of the saturable phase could be described by Michaelis-Menten kinetics (Table III-12). The V_{max}, the maximum rate of biotransformation, was determined to be 15.9 mg/kg/hr (164 umoles/kg/hr) for 1,1-DCE and 3.4 mg/kg/hr (35 umoles/kg/hr) for trans-1,2-DCE. Therefore, the relative rate of biotransformation was 1,1-DCE > trans-1,2-DCE. The atmospheric concentration, K_m, that causes transformation _in vivo_ in rats to occur at one-half the maximum biotransformation rate also was determined. The K_m was found to be 336 ppm (55.1 umoles/liter plasma) for 1,1-DCE and 411 ppm (183 umoles/liter plasma) for trans-1,2-DCE.

Based on kinetic analysis of DCEs in gas uptake studies, it has been suggested that the rate limiting step in biotransformation of DCEs at low concentration is blood flow to the liver (Andersen et al., 1980a). In addition, the concentration of an inhaled chemical in the blood is determined by pulmonary absorption. Since the weight-adjusted breathing volume decreases as body weight increases, the rate of uptake and therefore the rate of presentation of DCEs to the liver would be expected to be reduced to a similar degree. For a rat, the resting breathing volume is estimated to be 32 l/kg/hr. For a moderately active 70 kg human, the 8 hr work shift breathing volume is usually taken to be 10 m3, i.e., 18 l/kg/hr. Therefore, at lower exposure concentrations, less DCE would be presented to the

Table III-12

Inhalation Kinetic Constants for the Metabolism of DCEs Determined Using Gas Uptake Measurements

	V_{max}[a]		K_m[b]	
Chemical	(mg/kg/hr)	(umoles/kg/hr)	(ppm)	(umoles/liter plasma)
1,1-DCE	15.9	164	336	55.1
trans-1,2-DCE	3.4	35	411	183

[a] V_{max} is the maximum rate of metabolism.

[b] K_m is the atmospheric concentration that causes metabolism *in vivo* to proceed at half maximal velocity.

Based on Andersen et al., 1980a.

liver in the human relative to rats. It has therefore been suggested that, at low atmospheric concentrations, the biotransformation of DCEs would be slower in the human than in the rat. This would shift the K_m (ppm in atmosphere) to even higher concentrations for the human (Andersen et al., 1980a), if the V_{max}s were similar in each species.

Assuming that biotransformation of 1,1-DCE is limited by hepatic perfusion and pulmonary ventilation at low inhaled concentrations, the relative amounts of metabolites formed by different species can be calculated. Humans, on a per unit weight basis, would metabolize considerably less 1,1-DCE to toxic metabolites than would the rat or mouse. The data for 1,1-DCE biotransformation in mice and rats in Table III-7 can be extrapolated by reference to physiologic parameters to yield an estimate of the amount of biotransformation likely to occur in a human exposed to 10 ppm of 1,1-DCE for 6 hr. Ventilation is given by an equation of the form (Guyton, 1947):

$$Vt = 0.126\ \text{l/hr (body weight)}^{0.75}$$

For the mouse, rat and human (30 g, 250 g and 70 kg, respectively), Vt is 53.0, 31.7 and 7.75 l/hr respectively, for the animals at rest. In a 6 hr exposure to 10 ppm (0.0397 mg/l), the three species would inhale 12.81, 7.55 and 1.65 mg/kg, respectively. The data in Table III-7, for total transformed 1,1-DCE, show that the percent retained is 41% for the mouse and 38% for the rat. If a similar percent retained (about 40%) in humans, the human will biotransform only about 0.74 mg/kg. Assuming these assumptions are correct, the human would metabolize about

4-fold less than the rat (31.7/7.7 = 4.1) and about 7-fold less than the mouse (53.0/7.7 = 6.9).

IV. HUMAN EXPOSURE

A. 1,1-Diochloroethylene.

Humans may be exposed to 1,1-DCE in drinking water, food and air. Detailed information concerning the occurrence of and exposure to 1,1-DCE in the environment is presented in another document entitled "Occurrence of 1,1-Dichloroethylene in Drinking Water, Food, and Air" (Letkiewicz et al., 1983a). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food, and air.

This analysis is limited to drinking water, food, and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to 1,1-DCE from sources other than the three considered here, notably in occupational settings and from the use of consumer products containing 1,1-DCE. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little contol. Where one lives, works, and travels, what one eats, and physiologic characteristics related to age, sex, and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various 1,1-DCE concentrations. The 70-kg male is used for estimating intake.

a. Water

Cumulative estimated of the U.S populations exposed to various 1,1-DCE levels in drinking water from public drinking water systems are presented in Table IV-1. The values in the table were obtained using Federal Reporting Data Systems data on populations served by primary water supply systems (FRDS 1983) and the estimated number of these water systems that contain a given level of 1,1-DCE. An estimated 4,789,000 individuals (2.2% of the population of 214,419,000 using public water supplies) are exposed to levels of 1,1-DCE in drinking water at or above 0.2 ug/l, while 52,000 individuals (< 0.1%) are exposed to levels above 5 ug/l. It is estimated that no individuals are exposed to levels greater than 10 ug/l. Of the approximately 4.7 million people exposed to levels ranging from 0.2 to 5 ug/l, 2.4 million (52%) obtain water from surface water supplies. All exposure to 1,1-DCE in drinking water at levels above 5 ug/l is expected to be from groundwater sources.

No data were obtained on regional variations in the concentration of 1,1-DCE in drinking water. The highest concentrations are expected to occur near sites of production and use of 1,1-DCE.

Daily intake levels of 1,1-DCE from drinking water were estimated using various exposure levels and the assumptions presented in Table IV-2. The data in the table suggest that the majority of the persons using public drinking water supplies would be exposed to intake levels below 0.0057 ug/kg/day.

Table IV-1

Total Estimated Cumulative Population (in Thousands) Exposed to 1,1-Dichloroethylene in Drinking Water Exceeding the Indicated Concentration

System type	Number of people served in U.S. (thousands)	Cumulative population (thousands) exposed to concentrations (ug/l) of: ≥ 0.2	> 5	> 10
Ground water	73,473	2,347	52	0
Surface water	140,946	2,442	0	0
Total	214,419	4,789	52	0
(% of total)	(100%)	(2.2%)	(0.1%)	(0.0%)

Table IV-2

Estimated Drinking Water Intake of 1,1-Dichloroethylene

Exposure level (ug/l)	Persons using supplies exposed to indicated levels		Intake (ug/kg/day)
	Population	% of total population	
≥0.2	4,789,000	2.2%	≥0.0057
>5.0	52,000	0.1%	>0.14
>10	0	0.0%	>0.29

Assumptions: 70-kg man, 2 liters of water/day.

An indication of the overall exposure of the total population to 1,1-DCE can be obtained through the calculation of population-concentration values. These values are a summation of the individual levels of 1,1-DCE to which each member of the population is exposed. Population-concentration estimates for 1,1-DCE in drinking water are 1.2×10^6 ug/l x persons (best case), 1.3×10^7 ug/l x persons (mean best case), 5.3×10^7 ug/l x persons (mean worst case), and 6.4×10^7 ug/l x persons (worst case).

Assuming a consumption rate of 2 liters of water/day, population-exposure values of 2.4×10^6 ug/day x persons (best case), 2.6×10^7 ug/day x persons (mean best case), 1.1×10^8 ug/day x persons (mean worst case), and 1.3×10^8 ug/day x persons (worst case) were derived.

b. Diet

No data were obtained on levels of 1,1-DCE in foods. Therefore, the intake of 1,1-DCE from diet could not be estimated.

c. Air

Exposure to 1,1-DCE in the atmosphere varies from one location to another. The highest level of 1,1-DCE reported in the atmosphere was 27,000 ng/m^3 (Going and Spigarelli 1977 cited in Brodzinsky and Singh 1982). Normal levels, however, are lower. Brodzinsky and Singh (1982) calculated median air levels of 1,1-DCE for urban/suburban areas and source dominated areas of 20 ng/m^3 and 14,000 ng/m^3 (14 ug/m^3), respectively. Two data points for 1,1-DCE in rural/remote areas showed 0.0 ng/m^3 (Not Detected).

The monitoring data available are not sufficient to determine regional variations in exposure levels for 1,1-DCE. However, urban and industrial areas appar to contain higher levels, as expected.

The daily respiratory intake of 1,1-DCE from air was estimated using the asumptions presented in Table IV-3 and the median and maximum levels for 1,1-DCE reported above. The estimates in Table IV-3 indicate that the daily 1,1-DCE intake from air for adults in source dominated areas is approximately 4.6 ug/kg/day. The intake calculated using the maximum level reported is 8.9 ug/kg/day. The values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

SUMMARY

Table IV-4 presents a general view of the total amount of 1,1-DCE received by an adult male from air and drinking water. Four separate exposure levels in air and four exposure levels in drinking water are shown in the table. Since no data were obtained on levels of 1,1-DCE in foods in the United States, the contribution of 1,1-DCE in the diet to total 1,1-DCE exposure could not be assessed.

The data presented have been selected from an infinite number of possible combinations of exposure from each of the two sources. The actual exposures encountered would represent some finite subset of this infinite series of combinations. Whether exposure occurs at any specific combination of levels is now known; nor is it possible to determine the number of persons that would be exposed

Table IV-3

Estimated Respiratory Intake of 1,1-Dichloroethylene

Exposure (ug/m^3)	Intake (ug/kg/day)
Rural/remote (0.0)	0.0
Urban/suburban (0.020)	0.0066
Source dominated (14)	4.6
Maximum (27)	8.9

Assumptions: 70-kg man, 23 m^3 of air inhaled/day (ICRP, 1975).

Table IV-4

Estimated Intake of 1,1-Dichloroethylene from the Environment by Adult Males in ug/kg/day (% from Drinking Water)

Concentration in drinking water (ug/l)	Concentration in air			
	Rural/remote (0.0 ug/m^3)	Urban/suburban (0.27 ug/m^3)	Source dominated (1.2 ug/m^3)	Maximum (27 ug/m^3)
0	0.0 (--)	0.0066 (0%)	4.6 (0%)	8.9 (0%)
0.2[a]	0.0057 (100%)	0.012 (48%)	4.6 (0.1%)	8.9 (0.06%)
5.0[b]	0.14 (100%)	0.15 (93%)	4.7 (3.0%)	9.0 (1.6%)
10[c]	0.29 (100%)	0.30 (97%)	4.9 (45.9)	9.2 (3.2%)

Intake from each source:

Water:	0.2 ug/l:	0.0057 ug/kg/day
	5.0 ug/l:	0.14 ug/kg/day
	10 ug/l:	0.29 ug/kg/day
Air:	0.0 ug/m^3:	0.0 ug/kg/day
	1.020 ug/m^3:	0.0066 ug/kg/day
	14 ug/m^3:	4.6 ug/kg/day
	27	8.9 ug/kg/day
Food:	Not included	

[a] 4,789,000 individuals using public drinking water systems are estimated to be exposed to levels ≥ 0.2 ug/l (2.2% of population using public water supplies).

[b] 52,000 individuals using public drinking water systems are estimated to be exposed to levels > 5.0 ug/l (< 0.1% of population using public water supplies).

[c] No individuals using public drinking water systems are estimated to be exposed to levels > 10 ug/l.

to 1,1-DCE at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for 1,1-DCE by route of exposure. The relative dose received may vary from the relative intake. In addition, the relative effects of the chemical on the body may vary by different routes of exposure.

Brodzinsky and Singh (1982) calculated a median urban/suburban air level of 1,1-DCE of 0.020 ug/m^3 based on air monitoring data. Assuming an air level of 0.020 ug/m^3, drinking water would be the predominant source of 1,1-DCE exposure in the adult male at drinking water levels above 0.2 ug/l. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of 1,1-DCE in drinking water and low concentrations of 1,1-DCE in ambient air and food are unknown.

B. 1,2-Dichloroethylenes

Humans may be exposed to 1,2-DCE in drinking water, food, and air. Detailed information concerning the occurence of and exposure to 1,2-DCE in the environment is presented in another document entitled "Occurence of 1,2-Dichloroethylene in Drinking Water, Food and Air" (Letkiewicz et al., 1983b). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

Exposure Estimation

This analysis is limited to drinking water, food and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to 1,2-DCE from sources other than the three considered here, notably in occupational settings and from the use of consumer products containing 1,2-DCE. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various 1,2-DCE concentrations. The 70-kg male is used for estimating intake.

a. Water

Cumulative estimates of the U. S. populations exposed to various levels of cis- and trans-1,2-DCE in drinking water from public drinking water systems are presented in Table IV-5. The values in the table were obtained using Federal Reporting Data Systems data on populations served by primary

Table IV-5

Total Estimated Cumulative Population (in Thousands) Exposed to 1,2-Dichloroethylenes in Drinking Water Exceeding the Indicated Concentration[a]

System type	Number of people served in U.S. (thousands)	Cumulative population (thousands) exposed to concentrations (ug/l) of:					
		≥ 0.5	> 5	> 10	> 20	> 30	> 40
Ground water	73,473	2,934	477	352	352	176	0
Surface water	140,946	1,685	0	0	0	0	0
Total	214,419	4,619	477	352	352	176	0
(% of total)	(100%)	(2.2%)	(0.2%)	(0.2%)	(0.2%)	(0.1%)	(0.0%)

[a] Total estimated cumulatives are for total cis- and trans-1,2-dichloroethylene isomers.

water supply systems (FRDS 1983) and the estimated number of these water systems that contain a given level of 1,2-DCEs. An estimated 4,619,000 individuals (2.2% of the population of 214,419,000 using public water supplies) are exposed to levels of 1,2-DCEs in drinking water at or above 0.5 ug/l, while 477,000 individuals (0.2%) are exposed to levels above 5 ug/l. Of the approximately 4.1 million people exposed to levels ranging from 0.5 to 5 ug/l, 2.5 million (59%) obtain water from groundwater supplies. All exposure to 1,2-DCE in drinking water at levels above 5 ug/l is expected to be from ground water sources.

No data were obtained on regional variations in the concentration of 1,2-DCEs in drinking water. The highest concentrations are expected to occur near sites of production and use of 1,2-DCEs.

Daily intake levels of 1,2-DCEs from drinking water were estimated using various exposure levels and the assumptions presented in Table IV-6. The data in the table suggest that the majority of the persons using public drinking water supplies would be exposed to intake levels below 0.014 ug/kg/day.

An indication of the overall exposure of the total population to 1,2-DCEs can be obtained through the calculation of population-concentration values. These values are a summation of the individual levels of 1,2-DCEs to which each member of the population is exposed. Population-concentration estimates for 1,2-DCEs in drinking water were

Table IV-6

Estimated Drinking Water Intake of 1,2-Dichloroethylenes[a]

	Persons using supplies exposed to indicated levels		
Exposure level (ug/l)	Population	% of total population	Intake (ug/kg/day)
≥0.5	4,619,000	2.2%	≥0.014
≥5.0	477,000	0.2%	≥0.14
>10	352,000	0.2%	>0.29
>20	352,000	0.2%	>0.57
>40	0	0.0%	>1.1

[a] Estimated intake is for total cis- and trans-1,2-dichloroethylene isomers.

Assumptions: 70-kg man, 2 liters of water/day.

1.1×10^7 ug/l x persons (best case), 1.8×10^7 ug/l x persons (mean best case), 1.2×10^8 ug/l x persons (mean worst case), and 1.3×10^8 ug/l x persons (worst case).

Assuming a consumption rate of 2 liters of water/day, population-exposure values of 2.2×10^7 ug/day x persons (best case), 3.6×10^7 ug/day x persons (mean best case), 2.4×10^8 ug/day x persons (mean worst case), and 2.6×10^8 ug/day x persons (worst case) were derived.

b. Diet

No data were obtained on levels of 1,2-DCEs in foods in the United States. Therefore, no estimates of the daily intake of 1,2-DCEs from the diet could be made.

c. Air

Exposure to 1,2-DCEs in the atmosphere varies from one location to another. The highest level of cis-1,2-DCE reported in the atmosphere was 27,000 ng/m^3 (27 ug/m^3) (Pellizzari et al., 1979 cited in Brodzinsky and Singh, 1982). High levels, averaging greater than 3,000 ng/m^3 (3.0 ug/m^3), have been detected in other areas. Normal levels, however, are somewhat lower. Brodzinsky and Singh (1982) calculated median air levels of cis-1,2-DCE for rural/remove areas, urban/suburban areas, and source dominated areas of 0.0 ng/m^3 (0.0 ug/m^3), 270 ng/m^3 (0.27 ug/m^3), and 1,200 ng/m^3 (1.2 ug/m^3), respectively. trans-1,2-DCE was monitored at only one site at a level of 3,700 ng/m^3 (3.7 ug/m^3) (Pellizzari, 1978 cited in Brodzinsky and Singh, 1982).

The monitoring data available are not sufficient to determine regional variations in exposure levels for 1,2-DCEs. However, urban and industrial areas appear to contain higher levels, as expected.

The daily respiratory intake of cis-1,2-DCE from air was estimated using the assumptions presented in Table IV-7 and the median and maximum levels for cis-1,2-DCE reported above. The estimates in Table IV-7 indicate that the daily cis-1,2-DCE intake from air for adults in source dominated areas is approximately 0.4 ug/kg/day. In contrast, the intake calculated using the maximum level reported is 8.9 ug/kg/day; few if any persons are believed to be exposed at that level. The values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

SUMMARY

Table IV-8 presents a general view of the total amount of 1,2-DCEs received by an adult male from air and drinking water. Four separate exposure levels in air and six exposure levels in drinking water are shown in the table. No data were obtained on levels of 1,2-DCEs in foods; therefore, the relative contribution of 1,2-DCEs in the diet to total 1,2-DCEs exposure could not be assessed.

It should be noted that the intake of 1,2-DCEs from drinking water is based on data for both the cis- and trans-isomers, while the intake from ambient air is based on data for the cis isomer only. The intake of 1,2-DCEs from ambient air would be expected to be somewhat higher if both isomers were accounted for.

Table IV-7

Estimated Respiratory Intake of cis-1,2-Dichloroethylene

Exposure (ug/m3)	Intake (ug/kg/day)
Rural/remove (0.0)	0.0
Urban/suburban (0.27)	0.089
Source dominated (1.2)	0.39
Maximum (27)	8.9

Assumptions: 70-kg man, 23 m^3 of air inhaled/day (ICRP, 1975).

Table IV-8

Estimated Intake of 1,2-Dichloroethylenes from the Environment by Adult Males in ug/kg/day (% from Drinking Water)[a]

Concentration in drinking water (ug/l)	Concentration in air			
	Rural/remote (0.0 ug/m^3)	Urban/suburban (0.27 ug/m^3)	Source dominated (1.2 ug/m^3)	Maximum (27 ug/m^3)
0	0.0 (--)	0.089 (0%)	0.39 (0%)	8.9 (0%)
0.5[b]	0.014 (100%)	0.10 (14%)	0.40 (3.5%)	8.9 (0.16%)
5.0[c]	0.14 (100%)	0.23 (61%)	0.53 (26%)	9.0 (1.6%)
10[d]	0.29 (100%)	0.38 (76%)	0.68 (43%)	9.2 (3.2%)
20[e]	0.57 (100%)	0.66 (86%)	0.96 (59%)	9.5 (6.0%)
40[f]	1.1 (100%)	1.2 (92%)	1.5 (73%)	10 (11%)

Intake from each source:

Water: 0.5 ug/l: 0.014 ug/kg/day
5.0 ug/l: 0.14 ug/kg/day
10 ug/l: 0.29 ug/kg/day
20 ug/l: 0.57 ug/kg/day
40 ug/l: 1.1 ug/kg/day

Air: 0.27 ug/m^3: 0.089 ug/kg/day
1.2 ug/m^3: 0.39 ug/kg/day
27 ug/m^3: 8.9 ug/kg/day

Food: Not included

[a] Estimated intake is for total cis- and trans-1,2-dichloroethylene isomers.

[b] 4,619,000 individuals using public drinking water systems are estimated to be exposed to levels ≥ 0.5 ug/l (2.2% of population using public water supplies).

[c] 477,000 individuals using public drinking water systems are estimated to be exposed to levels > 5.0 ug/l (0.2% of population using public water supplies).

[d] 352,000 individuals using public drinking water systems are estimated to be exposed to levels > 10 ug/l (0.2% of population using public water supplies).

[e] 352,000 individuals using public drinking water systems are estimated to be exposed to levels > 20 ug/l (0.2% of population using public water supplies).

[f] No individuals using public drinking water systems are estimated to be exposed to levels > 40 ug/l.

The data presented have been selected from an infinite number of possible combinations of concentrations for the two sources. The actual exposures encountered would represent some finite subset of this infinite series of combinations. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to 1,2-DCEs at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes.

Brodzinsky and Singh (1982) calculated a median urban/suburban air level of 1,2-DCEs of 0.27 ug/m^3 based on air monitoring data. Assuming an air level of 0.27 ugm^3, drinking water would be the predominant source of 1,2-DCE exposure in the adult male at drinking water levels above 3.1 ug/l. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of 1,2-DCEs in drinking water and low concentrations of 1,2-DCEs in ambient air and food are unknown.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for 1,2-DCEs by route of exposure. The relative dose received may vary from the relative intake. In addition, the relative effects of the chemical on the body may vary by different routes of exposure.

V. HEALTH EFFECTS IN ANIMALS

A. Acute and Chronic Effects

Several studies on the acute oral toxicity (LD_{50}s) of the DCEs have been conducted (Jenkins et al., 1972; Andersen and Jenkins, 1977; Freundt et al., 1977; Jones and Hathway, 1978b; NIOSH, 1978; Andersen et al., 1979a; Ponomarkov and Tomatis, 1980). These data are summarized in Table V-1 and show a wide range of LD_{50} values. The use of different vehicles and the nutritional status and ages of the animals may partially account for the wide range of LD_{50} values.

Fasted animals were considerably more sensitive than were fed animals. Furthermore, acute toxicity was considerably more severe in rats given 1,1-DCE in corn oil or mineral oil than in 0.5% Tween 80 in water. The differences among effects of the vehicles could not be attributed to either the rate of fast-phase exhalation of 1,1-DCE or the total amount of 1,1-DCE exhaled or to the ability of the animals to detoxify the agent (Chieco et al, 1981).

1,1-Dichloroethylene. The lethality of 1,1-DCE in fasted rats was found to depend upon the size (age) of the animals. Large rats (395 g) had an oral LD_{50} (observed for 14 days following dosage) of > 1500 mg/kg, whereas smaller (73 g) rats had an LD_{50} of < 100 mg/kg (Andersen and Jenkins, 1977). The LD_{50} value for larger rats agreed with a previous study (Jenkins et al., 1972). The dose mortality curves for the fasted rats showed an extended plateau and then decreased at higher doses for young animals (73 g). Due to this unusual

Table V-1

Acute Toxic Effects of DCEs

Compound	Route	Species	Dose	Effect	Reference
1,1-DCE	oral	rat	200 mg/kg	LD_{50}	NIOSH, 1978
1,1-DCE	oral	rat rat[a]	>1500 mg/kg 84 mg/kg	LD_{50} LD_{50}	Jenkins et al., 1972 Jenkins et al., 1972
1,1-DCE	oral	rat (395 g) (fasted)	>1500 mg/kg	LD_{50}	Andersen and Jenkins, 1977
1,1-DCE	oral	rat (73 g) (fasted)	<100 mg/kg	LD_{50}	Andersen and Jenkins, 1977
1,1-DCE	oral	rat (male) rat (female)	1800 mg/kg 1500 mg/kg		Ponomarkov and Tomatis, 1980
1,1-DCE	oral	mouse (male)	217 mg/kg	LD_{50}	Jones and Hathway, 1978b
		mouse (female)	194 mg/kg		Jones and Hathway, 1978b
1,1-DCE	oral iv	dog dog	5750 mg/kg 225 mg/kg	LD_{50} LD_{50}	NIOSH, 1978 NIOSH, 1978
1,1-DCE	inhal	rat (fed)	15,000 ppm/4 hr	LC_{50}	Jaeger et al., 1974
	inhal	rat (fasted)	600 ppm/4 hr	LC_{50}	Jaeger et al., 1974
	inhal	rat (fasted)	200 ppm/4.1 hr 400 ppm/3.6 hr 500 ppm/13.0 hr 1000 ppm/2.4 hr 2000 ppm/1.4 hr	LC_{50}	Andersen et al., 1979a
1,1-DCE	inhal	rat (fed)	6350 ppm/4 hr	LC_{50}	Siegel et al., 1971
1,2-DCE	oral ip	rat mouse	770 mg/kg 2000 mg/kg	LD_{50} LD_{50}	NIOSH, 1978 NIOSH, 1978
trans-1,2-DCE	oral	rat (180-200 g)	1.0 ml/kg (1300 mg/kg)	LD_{50}	Freundt et al., 1977
	ip	rat (180-200 g)	6.0 ml/kg (7800 mg/kg)	LD_{50}	Freundt et al., 1977
	ip	mouse	3.2 ml/kg (4160 mg/kg)	LD_{50}	Freundt et al., 1977

[a] Adrenalectomized.

dose-response, the authors concluded that one could not unambiguously determine LD_{50} values for 1,1-DCE in younger rats (Andersen and Jenkins, 1977). It also was determined in this study that the amount of 1,1-DCE retained by immature fasted male rats increased linearly up to a total dose of 100 mg/kg. Above this level, a greater percentage of the dose was excreted by the lungs and a plateau effect was observed (Andersen and Jenkins, 1977).

The acute inhalation toxicity of 1,1-DCE also has been determined (Jaeger et al., 1974). A large difference in 24 hr LC_{50} values was found between fed (15,000 ppm) and fasted (600 ppm) rats after a 4 hr exposure. In another inhalation study on the toxicity of 1,1-DCE in mature male rats, the percent mortality that occurred in an exposure of 4 hr/day for 7 days increased from 0 to 50% in the concentration range from 100 to 200 ppm, but increased little over 50% as the concentration was increased from 200 to 2000 ppm, i.e., mortality was virtually independent of concentration (Andersen et al., 1979a). At higher concentrations, the mortality was related to the duration of exposure rather than to the ambient concentration.

Based on the above data, it has been suggested that the acute toxicity of 1,1-DCE is the result of a toxic metabolite and that this metabolite is formed by a saturable process (Andersen et al., 1979a, 1980b). Under inhalation exposure conditions above the metabolic saturation point, (ambient concentrations above 200 ppm) untransformed 1,1-DCE is readily excreted via the lung. Using data from kinetic studies, the acute inhalation toxicity in rats was shown to be a function of the amount of metabolite formed and not of the concentration of 1,1-DCE (Andersen et al., 1979b). Short term exposures produced mortality after formation of 25 to 30 mg of metabolite/kg. At concentrations between 200 to 1000 ppm, a direct correlation was found between the duration of an exposure required to kill rats (LT_{50}) and the time calculated to produce a constant amount of metabolite (Andersen et al., 1979b).

A comparative study of the lethality of 1,1-DCE in different species showed that inhalation of 60 ppm of 1,1-DCE for 2 days caused higher mortality in mice (8/10) than in rats (0/10) (Short et al., 1977a). This study also showed that there were similar values for the LC_{50} for 1 day exposures (22 to 23 hr/day) to 1,1-DCE in male (98 ppm) and female (105 ppm) mice. After repeated exposures, male mice were more sensitive to the lethal effects of 40 ppm of 1,1-DCE, since the mortality for males after day 3 (3/10) and day 5 (7/10) of exposure was higher than for females (0/10). Maltoni (1977) also demonstrated that species, strain and sex can greatly influence the toxic effects of 1,1-DCE, presumably due to the formation of differing amounts of toxic metabolites.

The effects of exposure to 1,1-DCE over a greater number of days also have been studied. Repeated exposure (20 days) of rats to 500 ppm of 1,1-DCE for 6 hr/day has been reported to cause nasal irritation, decreased body weight gain and liver cell degeneration, whereas only slight nasal irritation was noted for the same exposures to 200 ppm (Gage, 1970).

It also has been reported that liver and kidney damage occurred in animals exposed by inhalation for 8 hr/day, 5 days/week for several months at concentrations of 50 and 100 ppm of 1,1-DCE in air (Irish, 1963).

Continuous 90 day inhalation exposures to 0, 5, 15, 25 or 47 ppm (0, 20, 60, 99 or 187 mg/m^3) of 1,1-DCE or repeated daily exposures of 8 hr/day, 5 days/week for 6 weeks to 100 ppm (397 mg/m^3) were studied using rats, guinea pigs, dogs, rabbits and monkeys (Prendergast et al., 1967). Repeated exposures (30 exposures) to 100 ppm produced no mortality or visible toxic signs in any species. Hematologic and growth data did not reveal any evidence of a toxic response and histopathology was negative. In contrast to repeated intermittent exposures, continual exposure to 1,1-DCE caused increased mortality at concentrations as low as 5 ppm for guinea pigs and 25 ppm for monkeys. Growth depression was found in all species at the 47 ppm exposure level. Significant increases in serum glutamic-pyruvic transaminase (SGPT) and liver alkaline phosphatase were found in rats and guinea pigs exposed continually to the 47 ppm level, but these changes were not seen at the 5 ppm level. Enzyme levels were not determined at the 15 and 25 ppm levels. Histopathology revealed morphological changes in liver and kidneys of rats and guinea pigs at the 47 ppm exposure level, but not at 25 ppm or lower.

A study of the inhalation exposure to 60 ppm of 1,1-DCE for 22 hr/day for 7 days showed evidence for liver toxicity in both mice and rats as measured by increased levels of serum glutamic-oxaloacetic transaminase (SGOT) and SGPT (Short et al., 1977a,b).

Three deaths and 3 hepatic hemangiosarcomas were noted in an inhalation study in which 72 mice were exposed to 55 ppm of 1,1-DCE for 6 hr/day, 5 days/week for 12 months (Lee et al., 1978). Inflammatory, degenerative and mitotic changes were observed in most of the livers. Six mice had bronchioalveolar adenomas, but there were no mammary gland tumors. Exposure of rats to the same inhalation regimen resulted in slightly depressed body weights. Hemangiosarcomas occurred in the mesenteric lymph nodes or subcutaneous tissue in 2 of 72 exposed rats.

Dow Chemical Company has reported that daily oral administration of 1,1-DCE to dogs for 97 consecutive days at doses of 6.25, 12.5 or 25 mg/kg bw caused no adverse effects (Norris, 1977; Quast et al., 1983). The animals (4/sex/group) were given the compound as a 50% solution in peanut oil in a gelatin capsule. Each day, a control group of 4 animals/sex was given the same amount of peanut oil as the 25 mg/kg dose animals. The dogs were housed 4/pen.

The dogs were observed daily for toxicity, with food consumption/pen measured twice weekly, to calculate average daily consumption/animal. Hematological parameters measured on days -48 (48 days prior to start), +33 (33 days after start) and +84 were; packed cell volume, RBC count, hemoglobin concentration, total and differential white cell counts.

Urinalyses to measure specific gravity, sugar, protein, ketones, occult blood, bilirubin and microscopic examination of sediment were conducted on day +83 and at necropsy. Clinical chemistry, done after overnight fasting on days -7, +85 and +97, included blood urea nitrogen (BUN), SGPT, serum alkaline phosphatase (SAP), and SGOT. Non-protein free sulfhydryl (SH) content of liver and kidney was determined at necropsy, along with weights of the brain, liver, kidney, heart and testes, following overnight fasting. Ophthalmological exams were conducted on all animals at the start and end of the study. At necropsy, both eyes of each dog in the control and high dose groups were examined grossly and microscopically.

No exposure-related changes were observed in appearance, demeanor, body weights or food consumption. The mean white cell counts of male dogs receiving 6.25 or 25 mg/kg/day were 17 and 19%, respectively ($P < 0.05$), lower than control values on day +84. However, these values were not significantly different from their own pre-exposure white cell counts. In addition, they were within the range of normal values observed in that laboratory. Therefore, the investigators considered the differences to be unrelated to 1,1-DCE ingestion.

Female dogs receiving 6.25 mg/kg 1,1-DCE exhibited a statistically significant decrease in BUN levels at day -7 and an increase in SGPT at day +85 (38 ± 7 in controls vs 50 ± 6 in treated; $P < 0.05$). Males in that same dose group had elevated SGOT and SGPT values at sacrifice ($P < 0.005$) compared to their controls. However, the investigators stated that the values were within the range of normal values observed historically in that laboratory. No alterations in the clinical chemistry parameters were noted at the 12.5 or 25 mg/kg/day doses except for one high dose male that had an elevated SGPT on day +85, but not on day +97. No changes were seen in the SH content of the liver or kidneys.

No compound-related changes were reported in any of the parameters measured on urinalyses, in organ weight or organ:body weight ratios or on gross or microscopic examination of tissues. One male receiving 12.5 mg/kg/day had grossly enlarged kidneys, but no accompanying histopathology. The investigators concluded that this finding was not compound-related.

Results were reported from a 90 day toxicity study in rats given concentrations of 50, 100 or 200 ppm of 1,1-DCE in water or exposed for 6 hr/day, 5 days/week at initial levels of 0, 10 or 40 ppm 1,1-DCE in air (Rampy et al., 1977). After 5 weeks, the doses were increased to 25 or 75 ppm. There was also a separate study done at 0, 25 or 75 ppm.

Ten rats/sex/group were used, with 2 rats/sex/group sacrificed at days 1, 3, 10 and 30 for the determination of non-protein SH groups in the liver and kidney. The mean daily dosage levels in mg/kg based upon the amount of water consumed were 0, 7.5, 12.6 or 25.6 mg/kg for the females and 0, 5.9, 10 or 19 mg/kg for the males. Body weight was recorded once a week for the first month and monthly thereafter. Hematological and clinical chemistry measurements and urinalyses were conducted at 30 and 90 days. The parameters measured were the same as described in Quast et al. (1983).

Except for a decreased kidney:body weight ratio in males at the low dose, there were no statistically significant differences in organ weights or organ:body weight ratios at the termination of the study. The only histopathology noted was an increased cytoplasmic vacuolization of hepatocytes in livers of both sexes exposed to the highest dose. The investigators considered this to be a minimal change and reversible if the animals were removed from exposure to the chemical.

In the inhalation studies, there were no significant differences in organ weights at 30 or 90 days. Increased vacuolization in the liver was seen at both the 25 and 75 ppm exposure levels at 30 days and beyond. It was not seen in rats exposed to 10 or 40 ppm for only 30 days.

A 2 year chronic toxicity/oncogenicity study was conducted in rats given concentrations of 0, 50, 100 or 200 ppm of 1,1-DCE in drinking water (Rampy et al., 1977; Quast et al., 1983). In the interim report, the primary finding from this study was increased vacuolization of hepatocytes in the livers of animals in the high dose group (Rampy et al., 1977). Based on gross tumor count, tumor incidence was not greater than controls.

The time-weighted average in mg/kg/day were 0, 6, 10 or 20 for males and 0, 8, 13 or 26 for the females. Groups of 48 animals/sex/dose were used, except for controls (80/sex).

The animals were observed at least twice a week for overt toxicity, changes in appearance or behavior and tumor formation. Biweekly food consumption and daily water consumption were measured for the first 3 months; these determinations were made at periodic intervals thereafter. Body weights were recorded once a week for 14 weeks and monthly thereafter. Hematologic determinations and urinalyses were conducted on at least 5 rats/sex/group at 6, 12, 18 and 23 months. Clinical chemistry measurements were made on 5 rats/sex/group at 6, 12 and 18 months and on 10 rats/sex/group or all survivors if fewer than 10 remained at terminal necropsy. The parameters measured are the same as those described above for the subchronic rat study (Rampy et al., 1977).

At necropsy, following overnight fasting, the brain, heart, liver, kidney and testes were weighed. Gross and microscopic examination was done on complete sets of tissues (37) on all control and high dose animals. Only selected tissues from target organs and grossly recognizable neoplastic changes were examined microscopically from animals at the other two dose levels.

No consistent, dose-related changes were observed in any parameter measured. The only pathological finding considered by the investigators to be treatment-related was in the liver of animals of both sexes in the high-dose group. These microscopic changes, when present, were usually characterized by a minimal amount of mid-zonal hepatocellular fatty change. The degree of increase in this pathology was statistically significant in the males, while a trend toward an increase was seen at the intermediate dose. No exposure-related changes were seen in males at the low dose. Minimal hepatocellular swelling and fatty changes were detected in female rats at all dose levels. No significant treatment-related hepatocellular necrosis was evident in either sex at any dose.

cis- and trans-1,2-DCE. The LD_{50} values for 1,2-DCE (isomer mixture) and trans-1,2-DCE are shown in Table V-1 (Freundt et al., 1977). No similar data are available for the cis-isomer.

The trans- isomer of 1,2-DCE was administered *per os* to male CD-1 mice (9-10/group) for 14 days at levels of 0, 21 or 210 mg/kg (Barnes et al., 1985). The authors found no changes in body or organ weights or in serum chemistry values, but did observe reductions in fibrinogen level and prothrombin time in the 210 mg/kg/day group.

CD-1 mice (140/sex/dose) were given trans-1,2-DCE for 90 days in their deionized drinking water at levels of 17, 175 or 387 for males and 23, 224 or 452 mg/kg/day for females, while controls (260/sex) were given deionized water only (Barnes et al., 1985). There were no changes in fluid consumption (31-48/sex/dose), body weight gain (23-24/sex/dose) among the experimental groups. In male mice (24/dose), significant increases in serum alkaline phosphatase were noted at the two highest dose levels. In females (24/dose), the thymus weight, calcualted as % body weight, was significantly depressed at the 224 and 452 mg/kg/day doses, while the lung weight was decreased only at the highest dose.

Hayes et al. (1987) administered trans-1,2-DCE to Charles River CD rats (20/sex/dose) in their drinking water at levels of 402, 1,314 or 3,114 mg/kg/day to males and 353, 1,257 or 2,809 mg/kg/day to females. The authors found no compound-related effects on water consumption, terminal body weights, hematology, serum chemistry, urinalyses or histopathology. They did, however, report significant dose-dependent decreases in kidney weights and kidney weight ratios at the 1,257 and 2,809 mg/kg/day doses in the female rats.

The effects of short- and long-term inhalation exposure to trans-1,2-DCE have been investigated (Freundt et al., 1977). Adult female rats were exposed to 0, 200, 600 or 1000 ppm trans-1,2-DCE for 8 hr/day, 5 days/week for 16 weeks. The lowest dose produced histological evidence of slight to severe fatty degeneration of liver lobules and Kupffer cells. In addition, marked pulmonary hyperemia and alveolar septal distension were noted. Fibrous swelling of cardiac muscle also was observed. Exposure to 1000 ppm of trans-1,2-DCE for 8 hr caused a fall in serum albumin, BUN, SAP activity and number of erythrocytes, while 200 ppm for 8 hr was sufficient to lower leukocyte count. None of the exposure conditions investigated produced narcosis.

B. Specific Toxic Effects

1. Liver

The most common toxic effect of 1,1-DCE in rats, mice and guinea pigs was liver damage. Morphological changes appeared in fasted rats as early as 2 hr after the start of inhalation exposure to 200 ppm of 1,1-DCE (Reynolds et al., 1975). The parenchymal cell injury was characterized by the retraction of cell borders with the formation of pericellular "lacunae" which contained cytoplasmic projections, red blood cells and fibrin. Nuclear changes included loss of perinuclear chromatin and clumping and coalescing of perinuclear chromatin. Mitochondria appeared swollen, with ruptured outer membranes, while the endoplasmic reticulum was relatively normal. The injured mid-zonal parenchymal cells became confluent, forming a prominent midzonal stripe of necrosis which led to hemorrhagic centrilobular necrosis. In contrast to damage caused by 1,1-DCE, the characteristic morphological liver changes caused by exposure to other haloalkyls was damage to the endoplasmic reticulum. This suggests that 1,1-DCE exerted its toxic effects through a different mechanism than other haloalkyls (Reynolds et al., 1975).

The hepatotoxicity of 1,1-DCE has a complex dose-dependent response, with a threshold level, a concentration range of rapid increase, and an extended plateau where increasing doses caused little increase in toxicity. This threshold was lower for male rats (50 mg/kg) than for females (100 mg/kg) (Andersen and Jenkins, 1977).

Continual exposure of rats or guinea pigs to 47 ppm of 1,1-DCE for 90 days caused significant increases in SGOT and liver alkaline phosphatase activities, but these changes were not present at the 5 ppm level. Although no enzyme determinations were performed at the 15 and 25 ppm levels, histopathology revealed morphological changes in liver and kidneys of rats and guinea pigs at the 47 ppm exposure level, but not at 25 ppm or lower (Prendergast et al., 1967). Exposure of rats to 60 ppm of 1,1-DCE for 22 hr/day for 7 days caused increased levels of both SGOT and SGPT (Short et al, 1977a).

Oral administration of a single dose of 500 mg/kg of 1,1-DCE decreased liver glucose-6-phosphatase, but increased liver alkaline phosphatase (5-fold increase), liver tyrosine transaminase (11-fold increase), SAP and SGPT (Jenkins et al., 1972).

Fasted rats were more sensitive to both lethal and hepatotoxic effects 1,1-DCE. An increase in serum alanine alpha-ketoglutarate transaminase (same enzyme as SGPT) level was observed at 24 hr after a 4 hr exposure to 150 ppm in fasted rats, whereas a similar increase was observed in fed rats at ≥ 2000 ppm. Elevated SGPT preceded hepatic necrosis and death. This fed-fasted difference in SGPT elevation was also observed in isolated perfused rat liver (Jaeger et al., 1974). The increased susceptibility to liver injury has been attributed to decreased hepatic GSH concentration, which occurs after fasting (Jaeger et al., 1974; 1975a), after administration of some chemicals, e.g., diethyl maleate (Jaeger et al., 1974) or from normal diurnal variation (Jaeger et al., 1973a). The importance of GSH concentration is also shown by the observation that thyroidectomy, which causes an increase in GSH level, protects against hepatic injury and mortality from 1,1-DCE (Szabo et al., 1977). Conversely, pretreatment of animals with thyroxine was found to cause depletion of GSH and to increase hepatotoxicity (Jaeger et al., 1977b).

With regard to the difference in hepatotoxicity between fed and fasted rats, an *in vitro* study has shown that the activity of the enzymes of the MFO system is greatly enhanced in fasted rats, without a significant increase in the microsomal protein and cytochrome P-450 content. The *in vitro* rate of transformation of 1,1-DCE using microsomes obtained from fasted rats was twice the rate of microsomes from fed rats, suggesting that formation of increased amounts of metabolite may also play a role in the increased hepatotoxicity of 1,1-DCE in fasted rats (Nakajima and Sato, 1979).

The GSH level of the liver was shown to be decreased greatly following a 4 hr exposure of rats to 200 or 2000 ppm of 1,1-DCE and to rebound to higher than normal levels 24 hr after the end of the exposure (Jaeger et al., 1973a; Reynolds et al., 1975). However, the GSH level in the mitochondria was shown to remain depressed for 24 hr following exposure. Decreased uptake of O_2 by mitochondria isolated from rats exposed to 1,1-DCE paralleled the decrease in GSH in the mitochondria. Additionally, the serum levels of sorbitol dehydrogenase (SDH), an enzyme of cytoplasmic origin, and ornithine carbamoyl transferase, an enzyme of mitochondrial origin, were elevated concurrently. Both GSH depletion and reduced O_2 uptake occurred before serum enzyme levels increased.

An increase in total liver citric acid level also was found. Based on these observations, it has been suggested that 1,1-DCE may be oxidized by the MFO to monochloroacetic acid which is transformed further to a compound, possibly monochlorocitric acid, that inhibits mitochondrial activity and may be the basis for 1,1-DCE hepatotoxicity (Jaeger, 1977). Histochemical work has shown that exposure to 1,1-DCE caused a dramatic alteration in the pattern and a reduced staining intensity of the mitochondrial membrane markers, monoamine oxidase (MAO) and succinate dehydrogenase (Suc DH). These data were interpreted as suggesting the mitochondria as a major focus of injury (Chieco et al., 1981).

Further studies by Reynolds et al. (1980) have shown that exposure of fasted male Sprague-Dawley rats (150 to 200 g) to 200 ppm 1,1-DCE by inhalation for 1 to 4 hr resulted in a number of changes. Intracellular sodium levels began to rise during the first hr and preceded the morphologically apparent injury. When rats were given oral doses of 200 mg of 1,1-DCE/kg, the same effect was observed. In addition, striking decreases were observed in the centrilobular staining patterns of bile canalicular membrane Mg^{+2}-ATPase, outer mitochondrial MAO and inner mitochondrial membrane Suc DH and cytochrome oxidase (Chieco et al., 1982). Six hr later, responses included decreases in cytochrome P-450 and declines in mitochondrial K^{+}, marked imbalances in mitochondrial Na^{+}, Zn^{+2} and Mg^{+2} ion concentrations, increased serum transaminase activities, Ca^{+2} influx into cells and decreased staining of other plasma and mitochondrial membrane components. The authors concluded that plasma and mitochondrial membranes appear to be the primary foci of injury.

Although 1,1-DCE administration clearly decreases GSH levels *in vivo*, a single relatively high oral dose of 1,1-DCE (500 mg/kg po in corn oil) did not ($P > 0.05$) decrease levels of the glucuronidation cofactor, uridine diphosphate glucuronic acid, in livers of 7 fasted adult male Sprague-Dawley rats (Watkins and Klaassen, 1983).

The role of lipid peroxidation in hepatotoxicity by 1,1-DCE has been investigated. Whereas one study concluded that lipid peroxidation was not the mechanism of hepatic injury by 1,1-DCE (Jaeger et al., 1973b), another study showed that depletion of GSH in the liver by 1,1-DCE caused an increase in spontaneous lipid peroxidation (Younes and Siegers, 1980).

The role of metabolism in the toxicity of 1,1-DCE is not clear. Inducers and inhibitors of microsomal enzymes or xenobiotic substrates which would compete for biotransformation with DCEs have given conflicting results (Table V-2). Other factors such as age (weight) and nutritional status may also play a significant role (Andersen et al., 1978). It has been suggested that the conflicting data arise from the fact that the different pretreatment regimens interact with different sequential steps of a multi-step metabolic pathway or with different metabolic pathways (Andersen et al., 1978). It is also possible that different mechanisms may be responsible for lethality and hepatotoxicity (Reynolds and Moslen, 1977).

Table V-2

Results of Various Pretreatments on 1,1-DCE Effects in Rats

Pretreatment	Lethality	Hepatotoxicity	Metabolism	Reference
Microsomal Inducers				
Phenobarbital		decrease		Reynolds et al., 1975, 1977
Phenobarbital	increase	no change		Carlson and Fuller, 1972
Phenobarbital		decrease		Jenkins et al., 1972
Phenobarbital	decrease^a increase^b		no change	Andersen et al., 1978, 1979b
Phenobarbital			10% increase	Reichert and Henschler, 1978
3-Methylcholanthrene		no change		Reynolds et al., 1975
3-Methylcholanthrene	increase	no change		Carlson and Fuller, 1972
Aroclor 1254		decrease		Reynolds et al., 1975, 1977
Hexachlorobenzene		no change		Reynolds et al., 1975, 1977
DDT			35% increase	Reichert and Henschler, 1978
Spironolactone		no change		Reynolds et al., 1975, 1977
Pregnenolone-16-carbonitrile		no change		Reynolds et al., 1975, 1977
Microsomal Inhibitors				
SKF 525A	no change^a increase^b		no change	Andersen et al., 1978, 1979b
SKF 525A	increase	no change		Carlson and Fuller, 1972
SKF 525A			decrease	Reichert and Henschler, 1978
SKF 525A	no change	no change		Jaeger et al., 1975b
Pyrazole	decrease^c		84% decrease	Andersen et al., 1978, 1979b
3-Aminotriazole	decrease^c		65% decrease	Andersen et al., 1978, 1979b
CCl_4	decrease		92% decrease	Andersen et al., 1978, 1979b
Diethyl Dithiocarbamate	decrease	decrease		Short et al., 1977a, 1977b
Diethyl Dithiocarbamate		decrease	decrease	Siegers et al., 1979
Disulfiram	decrease	decrease		Short et al., 1977a, 1977b
Thiram	decrease	decrease		Short et al., 1977a, 1977b

---

[a] Small rats.
[b] Large rats.
[c] Rats of various sizes.

(continued on next page)

Table V-2 (Continued)

Pretreatment	Lethality	Hepatotoxicity	Metabolism	Reference
Competitive Substrates				
2,3-Epoxypropan-1-o1	increase		no change	Andersen et al., 1977, 1979b
Epichlorohydrin	increase			Andersen et al., 1980b
Styrene oxide	increase		decrease	Andersen et al., 1980b
Butadiene monoxide	increase		decrease	Andersen et al., 1980b
Competitive Substrates				
Cyclohexene oxide	increase		decrease	Andersen et al., 1980b
Diethyl maleate	increase		decrease	Andersen et al., 1980b
Cysteine	decrease	decrease		Jaeger et al., 1975b
Cysteine	decrease			Short et al., 1977b
Methionine	decrease			Short et al., 1977b
N-Acetyl cysteine	no change			Short et al., 1977b
Vitamin C	no change			Short et al., 1977b
Vitamin E	no change			Short et al., 1977b
Vinyl Chloride [d]		decrease	no change	Jaeger et al., 1975a
Free Radical Scavenger				
(+) Cyanindanol-3		decrease	no change	Siegers et al., 1979

---

[d] Administered simultaneously, not as a pretreatment.

However, one can conclude that the MFO inducers did not markedly potentiate the hepatotoxic effects of 1,1-DCE as they do for many halogenated hydrocarbons. This lack of effect might be attributable to the fact that the biotransformation of 1,1-DCE is limited by blood flow (Andersen et al., 1980a).

The microsomal enzyme inhibitor, SKF 525A, does not alter the hepatotoxic effects of 1,1-DCE, but it does increase 1,1-DCE lethality in larger rats. Also, it has been reported that pretreatment of rats with disulfiram or diethyldithiocarbamate reduces lethality, hepatotoxicity and the amount of covalently bound ^{14}C in livers of mice exposed to ^{14}C-1,1-DCE (Short et al., 1977a,b; Siegers et al., 1979). Disulfiram is known to reduce hepatic cytochrome P-450 levels, but it is also readily split into diethyldithiocarbamate which has SH groups that could react with toxic metabolites (Bartsch et al., 1979). This may be the mechanism by which it decreases hepatotoxicity. Similarly, cysteine and methionine have been shown to reduce the lethality and hepatotoxicity of 1,1-DCE (Jaeger et al., 1975b; Short et al., 1977b). Pretreatment with epoxides, which would decrease biotransformation of the toxic electrophilic intermediate, has been shown to increase hepatotoxicity (Andersen et al., 1977; 1980b). Simultaneous administration of vinyl chloride causes a decrease in hepatotoxicity, presumably by competing with the MFO metabolism of 1,1-DCE (Jaeger et al., 1975a). Pretreatment with antioxidants, such as vitamins C or E, did not effect lethality (Short et al., 1977b).

The hepatotoxicity of 1,2-DCEs, as determined by changes in hepatic enzymes, was studied and cis-1,2-DCE was found to be slightly more hepatotoxic than trans-1,2-DCE, but both appeared to be less toxic than 1,1-DCE (Jenkins et al., 1972). It has been reported that repeated inhalation exposures of rats to 200 ppm of trans-1,2-DCE for 8 hr/day, 5 days/week for 16 weeks produced fatty degeneration of the liver lobules and Kupffer cells (Freundt et al., 1977).

2. Kidney

Although renal lesions have been reported in studies at doses of 1,1-DCE similar to those causing hepatotoxicity, there has been less research in this area (Prendergast et al., 1967; Short et al., 1977a,b). The nephrotoxic effects of a single oral dose of 200, 400 or 600 mg/kg of 1,1-DCE have been examined in rats. Increases in BUN and plasma creatinine levels as well as increased kidney weight were found in males, but not in females, although both sexes had vacuolization, tubular dilatation and necrosis in the kidney (Jenkins and Andersen, 1978). The degree of covalent binding of 1,1-DCE metabolites has been shown to be higher in kidney than in liver in both rats and mice (McKenna et al., 1977; Short et al., 1977a). In addition, more water-soluble ^{14}C radioactivity was found in fasted than fed rats (Jaeger et al., 1977a). Inhalation exposure of mice and rats to 60 ppm for 23 hr/day for up to 5 days produced renal lesions in mice, but not in rats (Short et al., 1977b). The primary renal lesion observed after continuous exposure to 47 ppm for 90 days was nuclear hypertrophy of the renal tubular epithelium (Prendergast et al., 1967).

3. CNS

Like other chlorinated ethylenes, the DCEs would be expected to possess general anesthetic or narcotic properties. Although it has been reported that the primary effect of acute inhalation of 1,1-DCE is CNS depression, there are virtually no data characterizing either short-term or long-term effects of DCEs on the CNS (Irish, 1963).

Inhalation exposures of adult female SPF Wistar rats to trans-1,2-DCE, either 200 ppm for 8 hr/day, 5 days/week for 16 weeks or to 3000 ppm for a single 8 hr exposure, failed to produce pre-narcotic signs or narcosis (Freundt et al., 1977). The cis- isomer did not anesthetize rats in 4 hr at 8000 ppm, but at 16,000 ppm they were anesthetized in 8 min and killed in 4 hr (Irish, 1963).

Two studies on the behavioral toxicity of 1,2-DCE (identification of isomer(s) presented in experimental compound was not given in either study) have been published. Kallman et al. (1983) used taste aversion to saccharin in drinking water as an assay in male CD-1 mice. They reported that 1,2-DCE (given po in an emulsified mixture of water and vegetable oil) significantly increased ($P < 0.01$) saccharin aversion. At 145 mg/kg (95% confidence limit = 80 to 230 mg/kg), saccharin preference was reduced by 50%.

De Ceaurriz et al. (1983) used an assay in which male Swiss OF1 mice (20 to 25 g) were exposed to levels of 1500 to

2000 ppm 1,2-DCE by inhalation for 4 hr and then forced to swim in a restricted area. The characteristic period of immobility, designated as "behavioral despair," induced by placing the animals in a restricted swimming area can be affected by chemicals. Exposure to 1,2-DCE reduced this "despair" period in a dose-dependent manner.

4. Heart

Inhalation of 25,600 ppm 1,1-DCE by rats for 10 min has been found to sensitize the myocardium to both epinephrine-induced and nonepinephrine-induced arrhythmias. Since the cardiac sensitizing effects of 1,1-DCE were increased by phenobarbital pretreatment, a metabolite of 1,1-DCE may be responsible (Siletchnik and Carlson, 1974). However, none of the known metabolites sensitize the heart.

Inhalation of 3,000 ppm trans-1,2-DCE by rats for 8 hr was reported to produce fibrous swelling of the cardiac muscle and hyperemia which persisted for 14 hr after exposure (Freundt et al., 1977).

5. Pancreas

As reported for some other chlorinated hydrocarbon solvents, 1,1-DCE increases bile duct pancreatic fluid flow in fasted rats. The composition of the fluid did not differ significantly from that in control animals (Hamada and Peterson, 1977). The significance of this finding is unknown.

6. Immune System

trans-1,2-DCE was screened for potential immunological effects in CD-1 mice (Munson et al., 1982). Four-week old males were exposed for 14 consecutive days to the compound by gavage in a volume of 0.01 ml/g body weight at doses equal to 0.01 x LD_{50} (∼ 22 mg/kg) and 0.1 x LD_{50} (∼220 mg/kg). The LD_{50} for male mice was determined in range-finding studies to be 2,221 (range = 1,987 to 2,469) mg/kg. No changes in body weight or organ weight (liver, kidney, thymus, brain and lung) were observed.

Humoral immune response was assessed by measuring the number of IgM antibody-forming cells (AFC) to sheep RBCs. On the AFC/spleen basis, trans-1,2-DCE showed a trend towards producing immunosuppression ($P < 0.1$). Cell-mediated immune response was measured by quantifying the extravasation of human serum albumin during the delayed hypersensitivity response to sheep RBCs. trans-1,2-DCE had no effect at either dose (Munson et al., 1982).

Shopp et al. (1985) assessed humoral and cellular immune function in mice after 90 days of treatment with trans-1,2-DCE. The animals and exposure levels are the same as in the Barnes et al. (1985) study cited on page V-11. On day 4 after treatment, there was a significant decrease in AFC/spleen in only males (8-12/dose). When the data were calculated on the basis of spleen cells, the difference was significant only at the 175 and 387 mg/kg/day levels. The significance of the decrease in AFC/spleen in males at all three dose levels is uncertain. As mentioned, this decrease in AFC was seen at only the top two doses when the data were calculated on the basis of spleen cells and two other measures of humoral immunity, hemaglutination titers (11-16/dose) and spleen cell response to lipopolysaccharide (2-9/dose), were not affected at the 17 mg/kg/day dose level. Accordingly, the 17 mg/kg/day level is not to be considered an adverse effect. At the tested doses, this chemical did not exert an adverse effect on cell-mediated immune function.

7. Lung

Krijgsheld et al. (1983) administered 1,1-DCE to male C57BL/6J mice (ip, 125 mg/kg, in olive oil). Twenty-four hr later, they found a decrease in cytochrome P-450 and other enzymes in the lung microsomes. They also reported that necrosis was restricted to the non-ciliated bronchiolar epithelial (Clara) cells. Forkert and Reynolds (1982) administered 1,1-DCE (100 mg/kg po in mineral oil) to mice of the same strain. The Clara cells showed extensive dilation of cisternae and degeneration of the endoplasmic reticulum. However, 6 hr after a 200 mg/kg dose, both the Clara cells and the ciliated cells were necrotic and bronchiolar epithelial linings were exfoliated. After 24 hr, pulmonary edema, hemorrhage and focal atelectasis were present. Hypoxia also was noted at 24 hr. The lungs, however, completely recovered within 7 days. Forkert et al. (1982) also showed that dramatic changes in the subunit composition of pulmonary lactate dehydrogenase (LDH) isozymes occurred following po administration of 100 to 200 mg of 1,1-DCE/kg in mineral oil to the same strain of mice. (These changes in isozyme composition were not observed in kidney even though total LDH activity was decreased in that tissue). Thus, 1,1-DCE can cause pulmonary damage even when inhalation is not the route of administration.

C. Teratogenicity

The teratogenic potential of inhaled 1,1-DCE has been evaluated in rats and rabbits (Murray et al., 1979). Inhalation exposure for both species was for 7 hr/day at 20 (rats only), 80 or 160 ppm. Administration of 1,1-DCE to rats was on days 6 to 15 of gestation and on days 6 to 18 for rabbits. In rats, inhalation of 80 to 160 ppm of DCE produced significant maternal effects including decreased weight gain, decreased food consumption, increased water consumption and increased liver weight (160 ppm only). In the offspring, there was a significantly increased incidence of skeletal alterations at 80 to 160 ppm; these alterations included delayed ossification of various bones and wavy ribs. In rabbits, 160 ppm caused a significant increase in resorptions in the dams and a significant change in several minor skeletal variations in the offspring. In both rats and rabbits exposed to 1,1-DCE by inhalation, Murray et al. (1979) noted that concentrations which caused little evidence of maternal toxicity (20 ppm in rats and 80 ppm in rabbits) did not effect embryonal or fetal development.

The teratogenic potential of ingested 1,1-DCE also has been evaluated in rats (Murray et al., 1979). Drinking water containing 200 ppm 1,1-DCE, (approximately 40 mg/kg bw/day) was administered on days 6 to 15 of gestation. This concentration is near the upper limit of 1,1-DCE water solubility.

Data on maternal body weight gain, food and water consumption, and maternal liver weight showed no evidence for maternal toxicity. There were no effects on the average number of implantations, live fetuses or resorptions, and no alteration of the fetal sex ratio or body weight occurred. The only significant effect was an increase in mean fetal crown rump length and the authors concluded that 1,1-DCE was not teratogenic at this exposure level.

A study of the teratogenic potential of inhaled 1,1-DCE in rats and mice has been reported in an abstract (Short et al., 1976). Rats or mice were exposed for 23 hr/day from days 6 to 16 of gestation. The authors reported that no gross soft tissue or skeletal malformations attributable to exposure to 1,1-DCE were observed in rats exposed to up to 460 ppm or in mice exposed to 15 ppm.

D. Mutagenicity

1,1-DCE has been shown to be mutagenic in Salmonella typhimurium strains TA 1530, TA 100 (Bartsch et al., 1975; Simmon et al., 1977; Simmon and Tardiff, 1978) and TA 1535 (Jones and Hatnway, 1978c) and Escherichia coli K12 (Greim et al., 1975). In both bacterial systems, mutagenic activity required microsomal activation. Microsomal fractions derived from liver, kidney and lung of mice and rats were used to determine their relative ability to convert 1,1-DCE into mutagenic metabolites (Bartsch et al., 1975). Mouse liver, kidney and lung fractions were all effective, with liver showing the greatest activity (Table V-3). A much lower

Table V-3

Effect of Different Tissues on the *In Vitro* Bacterial Mutagenicity of 1,1-DCE

Species	Organ	Relative Activity
Mouse	Liver	100
	Kidney	20
	Lung	6
Rat	Liver	30
	Kidney	5
	Lung	3
Human[a]	Liver	20[b]

[a] Biopsy samples.

[b] Tissue samples were from 4 patients; relative activity for the individual patients was 11, 16, 17 and 38.

Based on Bartsch, 1976; Bartsch et al., 1976; Bartsch et al., 1979.

mutagenic response was observed in rats than in mice with liver and kidney fractions and there was only minimal activity with the lung fraction in either species. Human liver also was found to convert 1,1-DCE into mutagenic metabolites, its activity being similar to rat liver, but less than mouse liver (Bartsch, 1976).

Pretreatment of rats with modifiers of microsomal enzymes affected the bacterial mutagenicity of 1,1-DCE in the presence of S-9 fraction from liver from these animals (Table V-4). In general, microsomal enzyme inducers increased and inhibitors of microsomal P-450 decreased the mutagenicity of 1,1-DCE. Microsomal fractions derived from kidney and lung from animals pretreated with phenobarbital also increased the mutagenicity of 1,1-DCE (Bartsch et al., 1975).

At concentrations similar to those used for 1,1-DCE, both cis- and trans-1,2-DCE were non-mutagenic when assayed with *E. coli* K12 (Greim et al., 1975). It has been proposed that the mutagenic and presumably carcinogenic activities of chloroethylenes are related to the symmetry of the chlorine substitution of the epoxide intermediates formed by oxidation of the parent olefins. Compounds with unsymmetrical chlorine substitution would result in less stable, more reactive intermediates than symmetrically substituted materials (Henschler et al., 1976; Henschler, 1977; Henschler and Bonse, 1977). The above data support this hypothesis, at least with respect to mutagenesis in *E. coli* K12 systems. However, generalization of this hypothesis to carcinogenesis in intact animals is not possible.

Table V-4

Effect of Drug Treatment of Rats on Liver S-9 Mediated Bacterial Mutagenicity of 1,1-DCE

Drug Treatment	Relative Activity
None	100
Phenobarbital	200
Pregnenolone-16- -Carbonitrile	60
3-Methylcholanthrene	150
Aminoacetonitrile	40
Dibenamine	70
Disulfiram	10
Disulfiram (added *in vitro*)	10

Based on Bartsch et al., 1979.

In another bacterial study, both 1,1-DCE and cis-1,2-DCE were reported to be mutagenic in a host-mediated study using female ICR mice. The trans- isomer exhibited no activity (Cerna and Kypenova, 1977 Abst). Since this report is an abstract, few details are available. In addition, a computer search of the literature did not locate a publication by these authors on the DCEs. The Gene-Tox Agent Registry (U.S. EPA, 1986c) was also searched and no listings for cis-1,2-DCE could be located. Accordingly, the significance of this abstract cannot be determined.

1,1-DCE was tested for its ability to induce both point mutation (using the mutant allele ilv-92) and mitotic gene conversion (using the trp 5 locus) in the yeast *Saccharomyces cerevisiae* D7 in a suspension test with and without metabolic activation (Bronzetti et al., 1981). The chemical was tested at levels of 0, 10, 20, 30, 40 or 50 mM/plate, with a 2 hr exposure period. Without metabolic activation, 1,1-DCE was toxic at all levels, but not genetically active. When mouse liver 10,000 g activation system was added, concentration-dependent increases in both mutant and convertant frequencies were seen at concentrations above 20 mM. When compared to control levels, there were 5- and 9-fold increases in trp^+ and ilv^+ revertants, respectively, at the 50 mM 1,1-DCE treatment level. Although the authors did not include any statistical treatment, inspection of the mean revertant data and their respective standard deviations in the various treatment groups indicated that the treatment-related increases were significant.

In the intrasanguineous host-mediated assay, 0.2 ml of a saline solution containing 2 x 10^9 yeast cells/ml were injected into the retro-orbital sinus of male Swiss albino CD mice immediately prior to giving 400 mg of 1,1-DCE/kg orally. Four hr later, the animals were sacrificed and the yeast cells isolated. In this assay, the induction of gene conversion at the trp 5 locus was detected in liver and kidney; no significant increase was seen in the lungs. The same dose also induced ilv-92 reversion in the kidney and liver, but not the lung (Bronzetti et al., 1981).

Bronzetti et al. (1981) also gave 1,1-DCE by gavage (100 mg/kg in 0.5 ml corn oil for 5 days/week for 23 administrations followed by 200 mg/kg on the day of the assay; total dose = 2,500 mg/kg). As in the acute study described above, 0.2 ml of the yeast cells were given immediately prior to the administration of the last (200 mg/kg) dose of 1,1-DCE. An increased frequency of trp 5 conversions and ilv-92 reversions was seen in the liver and kidney, but not lungs.

Using ilv revertants and trp convertants as markers in _S_. _cerevisiae_ D7 strain, Galli et al. (1982a) reported that neither cis- or trans-1,2-DCE were genetically active. In the intrasanguineous host-mediated assay using mice (strain not specified), no genetic effects were noted after administering either cis- or trans-1,2-DCE (Galli et al., 1982b).

1,1-DCE was found to be non-mutagenic in V79 Chinese hamster cells in the presence of 15,000 g liver supernatant from phenobarbital-pretreated rats and mice (Drevon and Kuroki, 1979).

The DCEs were also tested for their ability to cause chromosome aberrations in female ICR mice. The 3 chemicals were given ip, once per day, at a concentration of one-sixth of their LD_{50} for 5 consecutive days. Cytogenetic analysis of bone marrow cells was then performed. Only cis-1,2-DCE treatment caused an increase in chromosomal aberrations (Cerna and Kypenova, 1977 Abst). As discussed on page V-29, the significance of this report is indeterminate.

The findings of adverse genetic effects in bacterial systems has not been confirmed in mammalian systems. Dominant lethal mutations were not found in CD-1 male mice exposed to 10, 30, or 50 ppm of 1,1-DCE for 6 hr/day for 5 days (Anderson et al., 1977). In this study there was a pre-implantation loss as reflected by an increase in the number of females that did not become pregnant after mating with exposed males (at the 50 ppm level only). However, there was no pre-implantation loss in those females that did become pregnant. In addition, post-implantation loss is more indicative of dominant lethality than is a pre-implantation loss. Similarly, adult CD male rats exposed to 55 ppm 1,1-DCE for 6 hr/day, 5 days/week for 11 weeks failed to produce dominant lethal mutations (Short et al., 1977c).

E. Carcinogenicity

The carcinogenicity of 1,1-DCE has been evaluated in gavage studies with rats and mice (NTP, 1982). The following discussion is, in large part, taken directly from the NTP Bioassay report.

A single dose range-finding study was conducted to determine the doses for the 14 day repeated dose study. 1,1-DCE was diluted in corn oil and administered by gavage to groups of 5 males and 5 females/species in doses of 0, 10, 50, 100, 500 or 1000 mg/kg. The animals were observed for 14 days and necropsied on Day 15. One female rat receiving 500 mg/kg died. One male rat that received 10 mg/kg died after 7 days and 2 that received 1000 mg/kg died within 48 hr. All male mice receiving 500 or 1000 mg/kg died. Among the female mice, 1/5 receiving 50 mg/kg, 3/5 receiving 500 mg/kg and 5/5 receiving 1000 mg/kg died.

Fourteen day repeated dose studies were conducted to determine the doses for the 90 day subchronic studies. Groups of 5 males and 5 females/species were administered 1,1-DCE in corn oil by gavage, daily for 14 days. On Day 16, all survivors were sacrificed and necropsied. Doses administered, survival and mean body weights of the dosed and control groups are shown in Tables V-5 and V-6.

Four of five male rats receiving 1,000 mg/kg, 3/5 female rats receiving 500 mg/kg or 1,000 mg/kg died within 48 hr. All were hyporeactive. Weight gain of male rats receiving 500 mg/kg was depressed 28%; the only surviving male rats receiving 1000 mg/kg lost weight. A dose-related decrease in mean body weight gain was observed in female rats. Weight gain was depressed 62% and 129% in females receiving 500 or 1000 mg/kg, respectively.

Table V-5

Dosage, Survival and Mean Body Weights of Rats Administered 1,1-DCE by Gavage for 14 Days

Dose (mg/kg)	Survival[a]	Mean Body Weights (grams) Initial	Final	Change[b]	Weight Change Relative to Controls (%)[c]
Male					
0	5/5	116.8 ± 6.57	163.4 ± 6.79	46.6 ± 7.77	----
10	5/5	110.6 ± 4.83	165.4 ± 9.24	54.8 ± 4.72	+ 17.6
50	5/5	112.0 ± 1.79	158.2 ± 4.39	46.2 ± 3.25	- 0.9
100	5/5	109.0 ± 4.68	151.8 ± 9.58	42.6 ± 9.11	- 8.6
500	5/5	114.0 ± 5.08	147.4 ± 2.25	33.4 ± 5.36	- 28.3
1000	5/5	118.0 ± 0.00	114.0 ± 0.00	-4.0 ± 0.00	- 108.6
Female					
0	5/5	94.6 ± 4.6	120.6 ± 8.62	26.0 ± 5.06	----
10	5/5	97.2 ± 3.47	126.2 ± 1.56	29.0 ± 2.39	+ 11.5
50	5/5	97.0 ± 3.16	121.6 ± 1.56	24.6 ± 4.02	- 5.4
100	5/5	97.4 ± 2.48	120.4 ± 3.14	23.0 ± 1.79	- 11.5
500	5/5	102.0 ± 6.00	112.0 ± 11.00	10.0 ± 5.00	- 61.5
1000	5/5	100.5 ± 0.50	93.0 ± 7.0	-7.5 ± 6.50	- 128.8

---

[a] Number surviving/number at start. All calculations are based on numbers surviving to end of study.

[b] Mean weight change of the survivors of the group ± standard error of the mean.

[c] Weight change of dosed survivors relative to survivors of the controls =

$$\frac{\text{Weight change (Dosed group) - Weight change (Control group) x 100}}{\text{Weight change (Control group)}}$$

From NTP, 1982.

Table V-6

Dosage, Survival and Mean Body Weights of Mice Administered 1,1-DCE by Gavage for 14 Days

Dose (mg/kg)	Survival[a]	Mean Body Weights (grams) Initial	Final	Change[b]	Weight Change Relative to Controls (%)[c]
Male					
0	5/5	22.2 ± 0.37	24.8 ± 0.37	2.6 ± 0.40	----
5	5/5	22.0 ± 0.32	23.4 ± 0.40	1.4 ± 0.40	- 46.2
10	5/5	23.0 ± 0.84	25.8 ± 0.86	2.8 ± 0.66	+ 7.7
50	5/5	22.2 ± 0.80	24.8 ± 0.97	2.6 ± 0.51	0.0
100	5/5	22.8 ± 0.37	24.0 ± 0.32	1.2 ± 0.20	- 53.8
500	0/5	d	d	d	
Female					
0	5/5	20.2 ± 0.20	21.6 ± 0.40	1.4 ± 0.40	----
5	5/5	20.6 ± 0.40	21.2 ± 0.20	0.6 ± 0.40	- 57.1
10	5/5	20.4 ± 0.40	21.0 ± 0.63	0.6 ± 0.60	- 57.1
50	5/5	20.4 ± 0.24	21.0 ± 0.32	0.6 ± 0.24	- 57.1
100	5/5	21.0 ± 0.32	22.2 ± 0.49	1.2 ± 0.73	- 14.3
500	0/5	d	d	d	

---

[a] Number surviving/number at start. All calculations are based on numbers surviving to end of study.

[b] Mean weight change of the survivors of the group ± standard error of the mean.

[c] Weight change of dosed survivors relative to survivors of the controls =

$$\frac{\text{Weight change (Dosed group)} - \text{Weight change (Control group)} \times 100}{\text{Weight change (Control group)}}$$

[d] No data are presented due to 100% mortality in this group.

From NTP, 1982.

All mice receiving 500 mg/kg died. Before death, they exhibited hyporeactivity, a staggering gait and rapid breathing. Hemorrhagic necrosis of the liver was seen at necropsy.

Ninety day subchronic studies were performed to determine the doses to be used in the chronic studies. Groups of rats and mice (10/species/sex) were administered 1,1-DCE in corn oil by gavage 5 times/week at 0, 5, 15, 40, 100 or 250 mg/kg for 13 weeks. Vehicle control groups consisting of 10 males and 10 females of each species received corn oil alone. After 90 days, survivors were sacrificed and necropsied.

Representative tissues from rats and mice receiving 250 mg/kg, from mice receiving 100 mg/kg and from control animals were examined microscopically. Livers from all other dose groups also were examined. The doses administered, survival and the mean body weights for rats and mice at week 13 are shown in Tables V-7 and V-8, respectively.

Although 3 female rats receiving 250 mg/kg died during the first week, no other rats died. Weight gain was depressed 20% for male rats receiving 250 mg/kg compared with controls.

Severe centrilobular necrosis of the liver was observed in the 3 female rats that died (Table V-9). Minimal to moderate hepatocytomegaly was seen in the rest of the rats that received 250 mg/kg. Lesser degrees (minimal to mild) of hepatocytomegaly were seen in 6/10 male rats and 3/10 female rats that received 100 mg/kg. Various combinations of portal and subcapsular fibrosis, bile duct hyperplasia, pigmented macrophages and hepatocellular atrophy were seen in all male

Table V-7

Dosage, Survival and Mean Body Weights of Rats Administered 1,1-DCE by Gavage for 13 Weeks

Dose (mg/kg)	Survival[a]	Mean Body Weights (grams) Initial	Final	Change	Weight Change Relative to Controls (%)[b]
Male					
0	10/10	118	316	+198	---
5	10/10	115	307	+192	- 3
15	10/10	115	306	+191	- 4
40	10/10	119	302	+183	- 8
100	10/10	117	299	+182	- 8
250	10/10	117	276	+159	-20
Female					
0	10/10	95	200	+105	---
5	10/10	93	193	+100	- 5
15	10/10	93	198	+105	0
40	10/10	97	194	+ 97	- 8
100	10/10	95	194	+ 99	- 6
250	7/10	97	190	+ 93	-11

[a] Number surviving/number at start. All calculations are based on numbers surviving to end of study.

[b] Weight change of dosed survivors relative to survivors of the controls =

$$\frac{\text{Weight change (Dosed group)} - \text{Weight change (Control group)} \times 100}{\text{Weight change (Control group)}}$$

From NTP, 1982.

Table V-8

Dosage, Survival and Mean Body Weights of Mice Administered 1,1-DCE by Gavage for 13 Weeks

Dose (mg/kg)	Survival[a]	Mean Body Weights (grams) Initial	Final	Change	Weight Change Relative to Controls (%)[b]
Male					
0	10/10	21	35	+14	---
5	10/10	21	35	+14	0
15	10/10	21	34	+13	- 7
40	9/10	21	33	+12	-14
100	8/10	21	30	+ 9	-36
250	0/10	21	--	--	--
Female					
0	10/10	18	24	+ 6	---
5	9/10	19	23	+ 4	-33
15	9/10	18	23	+ 5	-17
40	10/10	18	23	+ 5	-17
100	7/10	18	23	+ 5	-17
250	1/10	20	26	+ 6	0

[a] Number surviving/number at start. All calculations are based on numbers surviving to end of study.

[b] Weight change of dosed survivors relative to survivors of the controls =

$$\frac{\text{Weight change (Dosed group) - Weight change (Control group)} \times 100}{\text{Weight change (Control group)}}$$

From NTP, 1982.

Table V-9

Incidence of Liver Lesions in Rats and Mice Administered 1,1-DCE by Gavage for 13 Weeks

Dose (mg/kg)	Controls		5		15		40		100		250	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
Rats												
No. examined	9	10	10	10	10	10	10	10	10	10	10	10
Centrilobular necrosis	0	0	0	0	0	0	0	0	0	0	0	0
Fibrosis, pigmentation, bile duct hyperplasia, hepatocellular atrophy	0	0	0	0	0	0	0	0	3	4	10	7
Fatty metamorphosis	4	0	7	5	7	7	8	3	2	2	0	1
Hepatocytomegaly	0	0	0	0	0	0	1	0	6	3	10	7
Foci of cytoplasmic change	0	0	0	0	0	0	0	0	0	0	3	3
Mice												
No. examined	10	10	10	10	10	10	10	10	10	10	10	10
Cellular necrosis	0	0	0	0	0	0	0	0	2	2	5	5
Congestion	0	0	0	0	0	0	2	0	0	0	8	2
Necrosis, NOS	0	0	0	0	0	0	0	0	0	0	2	0
Cellular atypia	0	0	0	0	0	0	2	0	7	6	0	0
Fatty metamorphosis	0	0	0	1	2	0	2	2	0	0	0	0
Focal area of cellular	0	0	1	0	0	0	0	0	0	0	0	0

From NTP, 1982.

rats (mild to severe in 9/10 and minimal in the other) and in 7/10 female rats (mild to moderate in 6/10 and minimal in 1/10) receiving 250 mg/kg. The rats receiving 100 mg/kg were affected to a much lesser degree. Foci of cytoplasmic changes, primarily clear cell foci, were seen in 3/10 males and 3/10 females receiving 250 mg/kg. Fatty metamorphosis and/or cytoplasmic vacuolization (usually in minimal or mild degrees of severity), occurred in the animals of most groups, but had no dose relationship.

Original examination of the lesions in the rat livers placed more emphasis on the changes seen in the animals at the lower doses, whereas a review interpreted these changes to be less important. In retrospect, the 1,1-DCE doses of 1 and 5 mg/kg, based upon hepatotoxic effects, selected for the chronic study were probably too low.

All male mice receiving 250 mg/kg died within 24 hours; 9/10 females receiving 250 mg/kg died within 48 hours. Deaths occurred in 1/10 females receiving 5 mg/kg; and 2/10 males and 3/10 females receiving 100 mg/kg. A dose-related decrease in body weight gain was observed for male mice.

Centrilobular necrosis, hemorrhage and congestion of the liver were observed in male and female mice that died in the 250 mg/kg group (Table V-9). Cellular atypia of the liver (less severe than that seen in the rats) was observed in 7/10 males and 6/10 females receiving 100 mg/kg, but not in animals receiving 250 mg/kg. At 40, 15 and 5 mg/kg, the severity of hepatic lesions was dose-related. The incidence of hepatic lesions in males was dose-related and higher than in the females. The most frequently encountered change in mice exposed at 40 mg/kg or less was slight, sometimes moderate, fatty metamorphosis. Patchy foci or a few smaller cells with sparse cytoplasm were encountered much less frequently in mice than in rats. Hepatic effects were considered to be minimal at 5 mg/kg and doses selected for the mice for the chronic study were 2 and 10 mg/kg.

In the chronic study, rats and mice were grouped 50 sex/group with controls receiving corn oil alone. Rats were dosed at 1 or 5 mg/kg, mice at 2 or 10 mg/kg. Doses were administered 5 times per week by gavage for 104 weeks.

The animals were examined twice daily for morbidity and mortality and weighed every 2 weeks. At necropsy, gross and microscopic examinations were performed on major tissues, major organs and all gross lesions from sacrificed animals and those found dead. Mean body weights of dosed and control rats of either sex were comparable throughout the study. No compound-related clinical signs were observed.

While no significant differences in probability of survival were observed in any group, 12 control and 10 low-dose males died as a result of a 5 hr temperature excursion during week 82 of the study and 1 low-dose male was accidentally killed during week 42. These animals were censored in the survival analysis, but were examined histologically.

In male rats, 20/50 (40%) of the vehicle controls, 24/50 (48%) of the low dose and 37/50 (74%) of the high dose group survived to the end of the study. In the females, 27/50 (54%) of the vehicle controls, 28/50 (56%) of the low dose and 29/50 (58%) of the high dose group lived to the end of the study.

The number of accidental deaths may have influenced the incidence of late appearing tumors in the control and low dose males. However, the tumors, common to aging rats, occurred at comparable rates in control and treated animals and were not considered to be treatment-related.

Several non-neoplastic lesions of possible significance were observed. The incidence of chronic inflammation of the kidney in both male and female rats was higher in the high dose groups than in the controls [males: controls = 26/50 (52%); low dose = 24/48 (50%); high dose = 43/48 (90%) -- females: controls = 3/49 (6%); low dose = 6/49 (12%); high dose = 9/44 (20%)]. Although the occurrence of chronic nephritis appears to be dose-related, this lesion is common in aging rats.

All of the increased tumor incidences that were statistically significant by the Fisher exact test or by the Cochran-Armitage linear trend test were not significant when life table analyses were used. This difference occurs when life table analyses adjust for intercurrent mortality and thus minimize the impact of animals dying before the onset of late-appearing tumors. This adjustment was particularly critical for the analyses of tumor incidence in male rats because of the accidental deaths among this group.

Among the mice, the mean body weights of dosed male mice were lower than those of the controls; however, mean body weights of high dose and control females were comparable. Mean body weights of low dose mice of either sex were lower than those of high dose or control mice. No compound-related clinical signs were observed.

No significant differences in survival were observed between any groups of male mice. A significant reduction in the survival of female mice was observed in the low dose group as compared with the high dose group.

In male mice, 33/50 (66%) of the vehicle controls, 35/50 (70%) of the low dose and 36/50 (72%) of the high dose group survived to the end of the study. In female mice, 40/50 (80%) of the vehicle controls, 32/50 (64%) of the low dose and 42/50 (84%) of the high dose groups lived to the end of the study.

Necrosis of the liver (focal, multifocal and diffuse) were observed more frequently in dosed male mice than in controls [males: controls = 1/46 (2%); low dose = 3/46 (7%) and high dose = 7/49 (14%) -- females: controls = 0/47 (0%); low dose = 4/49 (8%) and high dose = 1/49 (2%)]. The incidence of lung inflammation was slightly below that normally seen in 2-year old B6C3Fl mice.

Neoplastic lesions observed in treated mice were considered to be unrelated to the administration of 1,1-DCE. The only observed significant ($P < 0.05$) increase in tumor incidence occurred in low dose female mice: lymphoma (2/48, 9/49, 6/50) and lymphoma or leukemia (7/48, 15/49, 7/50). Because similar effects were not found in the high dose female mice or male mice or rats of either sex, these increases were not considered to be related to 1,1-DCE treatment.

It was concluded by NTP that, under the conditions of this bioassay, 1,1-DCE administered by gavage was not carcinogenic for F334 rats or B6C3F1 mice of either sex. They also stated that since the use of the maximum tolerated dose in this study had not been clearly demonstrated and since previously reported studies have shown that carcinogenicity is associated with inhalation exposure to 1,1-DCE, this study should not be taken as proof that the chemical is not a carcinogen.

Additional studies of the potential carcinogenicity of 1,1-DCE have been conducted with mice, rats and hamsters using either oral administration or inhalation exposure. Preliminary results after a total of 98 weeks' observation have been reported (Maltoni, 1977; Maltoni et al., 1977). In the inhalation study, Swiss mice were exposed to 10 or 25 ppm of 1,1-DCE for 4 hr/day, 4 or 5 days/week for 52 weeks and then observed for the remainder of the study (Tables V-10 and V-11). Exposure to 10 ppm of 1,1-DCE caused no statistically significant increase in the incidence of any tumor. At 25 ppm, 17 of the mice exposed to 1,1-DCE had developed kidney adenocarcinomas compared to none in the control group (Table V-10). The majority of the tumors were observed in male mice. In contrast, no kidney adenocarcinomas were observed in Sprague-

Table V-10

Kidney Adenocarcinomas in Swiss Mice Exposed to 1,1-DCE via Inhalation[a]

1,1-DCE, ppm	Sex	Total Animals at Risk[b]	No Animals With Adenocarcinoma	%
0	Male[c]	54	0	0
0	Female[c]	49	0	0
0	Male[d]	46	0	0
0	Female[d]	52	0	0
10	Male[d]	22	0	0
10	Female[d]	20	0	0
25	Male[c]	78	16	20.5
25	Female[c]	65	1	1.5

[a] 4 hr/day, 4 to 5 days/week for 12 months.

[b] Defined here as the number of animals that had died since the appearance of the first tumor; or (survivors at the time of the first tumor) - (survivors at the time these preliminary data were reported).

[c] Animals were 9 weeks of age at start of exposure.

[d] Animals were 16 weeks of age at start of exposure.

Based on Maltoni et al., 1977.

Table V-11

Incidence of Mammary Adenocarcinomas in Female Swiss Mice Receiving 1,1-DCE via Inhalation[a]

	1,1-DCE Concentration, ppm			
	0	10	0	25
Age at start of test (weeks)	16	16	9	9
Number with tumors/ number at risk[b]	2/52	1/20	0/49	7/65
Incidence (%)	3.8	5.0	0	10.8
P values[c]	---	0.63	---	0.017

[a] 4 hr/day, 4 to 5 days/week for 12 months.

[b] Number at risk defined here as the number of animals that had died since the appearance of the first tumor (a kidney adenocarcinoma); or (survivors at time of the first tumor) - (survivors at the time these preliminary data were reported).

[c] Calculated using Fisher exact test and matched control incidence.

Based on Maltoni et al., 1977.

Dawley rats under the same regimen at exposures of up to 200 ppm. This study also showed a significant increase in mammary adenocarcinoma in Swiss mice inhaling 25 ppm (Table V-11) and in Sprague-Dawley rats inhaling 100 or 150 ppm of 1,1-DCE (Table V-12) (Maltoni et al., 1977). At 10, 25 or 50 ppm of 1,1-DCE, there was no increase in tumor incidences in Sprague-Dawley rats. Oral administration of 20 mg/kg of 1,1-DCE (4 to 5 days/week for 52 weeks) to female Sprague-Dawley rats resulted in a 42% incidence of mammary tumors, whereas controls had a 34% incidence (not statistically significant).

Hamsters exposed by inhalation to 25 ppm of 1,1-DCE did not exhibit an increased tumor incidence (Maltoni, 1977; Maltoni et al., 1977). Additionally, it has been reported indirectly that other studies by Maltoni found no statistically significant increased incidence of any tumor in BALB/c, C56BL, or C_3H mice (Fishbein, 1979).

In another inhalation study (Lee et al., 1978), CD-1 mice and CD rats were exposed to 55 ppm of 1,1-DCE for 6 hr/day, 5 days/week for 7 to 12 months. Hepatic hemangiosarcomas were observed in the mice exposed to 1,1-DCE: 2/35 for males and 1/35 for females in the treated group compared to 0/26 for males and 0/36 for females in the control group. Since these tumors have been reported to occur spontaneously, their significance was questioned. However, 2 rats developed hemangiosarcomas in the mesenteric lymph node or subcutaneous tissue that were judged probably to be caused by 1,1-DCE. The kidney pathology revealed no indication of adenocarcinoma.

Table V-12

Incidence of Mammary Tumors in Sprague-Dawley Rats Inhaling 1,1-DCE

	1,1-DCE Concentration, ppm					
	0	10	25	50	100	150
$\frac{\text{Number with tumors}}{\text{Number initially}}$	32/100	15/30	12/30	15/30	18/30	35/60
Incidence (%)	32	50	40	50	60	58
P values[b]	--	0.058	0.27	0.058	0.0058	0.001

[a] 4 hr/day, 4 to 5 days/week for 12 months.

[b] Calculated using the Fisher exact test.

Based on Maltoni et al., 1977.

An inhalation study using both Wistar rats and Sprague-Dawley rats has been reported (Viola and Caputo, 1977). Exposures were to 1,1-DCE concentrations from 75 to 200 ppm for 4 hr/day, 5 days/week for 12 months. The data were interpreted as showing no grossly observable correlation between tumor production and 1,1-DCE inhalation (Table V-13).

Additionally, male and female Sprague-Dawley rats were exposed to 1,1-DCE by inhalation (25 or 75 ppm for 6 hr/day, 5 days/week for 18 months). In the interim report (Rampy et al., 1977), there was no evidence of increased tumor incidence in animals treated with 1,1-DCE. The data are summarized in Table V-14. The only adverse effects found were minimal microscopic changes in the liver with a higher incidence at 75 ppm than at 25 ppm. In all other respects, there were no observed differences between control and treated groups.

The effect of weekly oral administration of 50 mg/kg of 1,1-DCE following in utero exposure (150 mg/kg on day 17 of gestation) was studied in BDIV rats (Ponomarkov and Tomatis, 1980). The oral administration was continued for 120 weeks. There was no statistically significant increase in the total number of tumor bearing animals. However, an increased incidence of tumors at certain sites was observed: liver tumors in females and meningiomas in males. Additionally, hyperplastic nodules of the liver were observed in both male and female rats; these were not seen in control animals (Table V-15). The authors concluded that the results provided limited evidence of carcinogenicity of 1,1-DCE.

Table V-13

Incidence of Tumors in Rats Inhaling 1,1-DCE[a]

1,1-DCE, ppm	Sex	Number of Rats	Number of Tumor-Bearing Animals	% of Total	Types of Tumors
Wistar Rats					
0	M	30	5	17	Abdominal cavity (5)
0	F	30	10	33	Abdominal cavity (9) Lung (1)
b	M	51	8	16	Abdominal cavity (7) Liver (1)
b	F	23	9	39	Abdominal cavity (8) Lung (1)
Sprague-Dawley Rats					
0	M	30	0	0	
0	F	30	15	50	Subcutaneous fibromas (15)
75	M	16	1	6	Subcutaneous fibromas (1)
75	F	21	9	43	Subcutaneous fibromas (9)
100	M	30	3	10	Abdominal lymphomas (3)
100	F	30	17	57	Subcutaneous fibromas (16) Abdominal lymphoma (1)

a 4 hr/day, 5 days/week for 12 months.

b Exposure to 200 ppm for first 5 months, then reduced to 100 ppm.

Based on Viola and Caputo, 1977.

Table V-14

Grossly Observed Tumors in Sprague-Dawley Rats Inhaling 1,1-DCE[a]

Sex	Tumors	Exposure Level (ppm)	No. animals with tumor[b]	No. animals in group	Tumors,%
M	Subcutaneous tumor (Mammary or midcervical region)	Control	8/6	86	7.0
		75	9/8	85	9.4
		25	8/7	86	8.1
M	Subcutaneous tumor (eye, ear or head region)	Control	2	86	2.3
		75	2	85	2.4
		25	5	86	5.8
M	Subcutaneous tumor (body or limb region	Control	1	86	1.2
		75	4	85	4.7
		25	3	86	3.5
M	Liver nodule (tumor or mass)	Control	1	86	1.2
		75	2	85	2.4
		25	0	86	0
M	Kidney (primary site)	Control	3	86	3.5
		75	0	85	0
		25	0	86	0
F	Subcutaneous tumor (Mammary or midcervical region)	Control	138/68	86	79.1
		75	159/74	84	88.1
		25	149/73	88	82.9
F	Subcutaneous tumor (eye, ear or head region)	Control	1	86	1.2
		75	1	84	1.2
		25	0	88	0
F	Subcutaneous tumor (body, limb region)	Control	2	86	2.3
		75	1	84	1.2
		25	2	88	2.3
F	Liver nodule (tumor or mass)	Control	2	86	2.3
		75	1	84	1.2
		25	0	88	0
F	Kidney (primary site)	Control	1	86	1.2
		75	1	84	1.2
		25	1	88	1.1

[a] 6 hr/day, 5 days/week for 18 months.

[b] Where two numbers appear, data represent number of tumors over number of animals with tumors. Percentage is based on number of animals with tumors.

Based on Rampy et al., 1977.

Table V-15

Tumor Incidence in BDIV Rats Treated Weekly with 1,1-DCE

	Dose of 1,1-DCE, mg/kg			
	0		50	
	Male	Female	Male	Female
Effective number of rats[a]	49	47	81	80
Tumor-bearing rats				
Number	16	24	31	53
%	32.7	51.1	38.3	66.3
Number of tumors				
Total	16	29	35	64
Per Rat	0.3	0.6	0.4	0.8
Animals with more than one tumor				
Number	0	5	4	11
%	0	10.6	4.9	13.8
Distribution of tumors				
Meninges				
Number	1	0	6	0
%	2.0	0	7.4	0
Oral cavity				
Number	2	1	5	1
%	4.1	2.1	6.2	1.3
Stomach				
Number	0	1	1	2
%	0	2.1	1.2	2.5
Liver				
Number	0	0	1	3
%	0	0	1.2	3.8
Soft tissue				
Number	4	0	9	7
%	8.2	0	11.1	8.8
Mammary gland				
Number	0	22	1	39
%	0	46.8	1.2	48.8
Ovary				
Number	0	3	0	6
%	0	6.4	0	7.5
Other				
Number	9	2	12	6
%	18.4	4.3	14.8	7.5
Liver hyperplastic nodules				
Number	0	0	2	6
%	0	0	2.5	7.5

The percentage and the number of tumors are expressed in relation to the effective number of rats.

[a] Survivors at the time the first tumor were observed.

Based on Ponomarkov and Tomatis, 1980.

Male and female Sprague-Dawley rats were exposed to 1,1-DCE in drinking water at 60, 100 or 200 ppm for 2 years, corresponding to average daily doses of 7, 10 or 20 mg/kg/day for males and 9, 14 or 26 mg/kg/day for females (Rampy et al., 1977; Quast et al., 1983). Details of the protocol are described in Section A of this chapter. Data from the interim report of this study (Rampy et al., 1977) showed no evidence of increased tumor incidence in animals treated with 1,1-DCE (Table V-16). No adverse effect was observed in any of the treated groups with 2 exceptions. The 60 ppm female group had a statistically higher incidence of pituitary gland adenomas than the control animals. However, this was not considered to be a treatment effect, since it was not dose-related and Sprague-Dawley rats have a high and variable spontaneous incidence of this tumor. The other effect was a statistically significant dose-related incidence of liver lesions, described as fatty degeneration which was more marked in females than in males. Accompanying this was atrophy of the centrilobular cells and hypertrophy of the periportal liver cells. Treatment-related necrosis of cells was not observed.

The carcinogenic effects of 1,1-DCE also were investigated in Ha:ICR Swiss mice by several routes of administration Van Duuren et al., 1979). 1,1-DCE was inactive as a whole mouse skin carcinogen and inactive by subcutaneous injection. In the two stage carcinogenesis assay using phorbol myristate acetate (PMA) as a promoter, 1,1-DCE administered as a single dose of 121 mg was shown to be active as a skin tumor initiator.

Table V-16

Grossly Observed Tumors in Sprague-Dawley Rats
Given 1,1-DCE[a] in Drinking Water

Sex	Tumors	Dose (ppm)	No. animals with tumor[b]	No. animals in group	Tumors, %
M	Subcutaneous tumor (mammary or midcervical region)	Control	6/6	80	7.5
		200	6/4	47	8.5
		100	6/6	48	12.5
		60	6/6	48	12.5
M	Subcutaneous tumor (eye, ear or head region)	Control	4	80	5.0
		200	2	47	4.3
		100	0	48	0
		60	1	48	2.1
M	Subcutaneous tumor (body or limb region)	Control	2	80	2.5
		200	0	47	0
		100	0	48	0
		60	2	48	4.2
M	Nodular proliferation in liver (primary site)	Control	5	80	6.3
		200	0	47	0
		100	1	48	2.1
		60	1	48	2.1
M	Liver (Metastatic foci)	Control	0	80	0
		200	0	47	0
		100	0	48	0
		60	1	48	2.1
M	Liver (diffuse tumor infiltrate and enlarged, associated with lymphoid)	Control	0	80	0
		200	0	47	0
		100	1	48	2.1
		60	2	48	4.2
M	Kidney (primary site)	Control	2	80	2.5
		200	0	47	0
		100	0	48	0
		60	2	48	2.1
F	Subcutaneous tumor (mammary or midcervical region)	Control	104/59	80	73.7
		200	64/36	48	75.0
		100	68/27	48	77.1
		60	71/40	48	83.3
F	Subcutaneous tumor (eye, ear and head region)	Control	1	80	1.3
		200	1	48	2.1
		100	2	48	4.2
		60	1	48	2.1

(Continued next page)

Table V-16 (Continued)

Sex	Tumors	Dose (ppm)	No. animals with tumor[b]	No. animals in group	Tumors,%
F	Subcutaneous tumor (body or limb region)	Control	0	80	0
		200	0	48	0
		100	1	48	2.1
		60	0	48	0
F	Nodular proliferation in liver (primary site)	Control	2	80	2.5
		200	3	48	6.3
		100	0	48	0
		60		48	4.2
F	Liver (metastatic foci)	Control	1	80	1.3
		200	0	48	0
		100	0	48	0
		60	0	48	0
F	Liver (diffuse tumor infiltrate and enlarged, associated with lymphoid)	Control	2	80	2.5
		200	0	48	0
		100	0	48	0
		60	0	48	0
F	Kidney (primary site)	Control	1	80	1.3
		200	0	48	0
		100	1	48	2.1
		60	0	48	0

---

[a] Where two numbers appear, data represent number of tumors over number of animals with tumors. Percentage is based on number of animals with tumors.

Based on Rampy et al., 1977.

These data are not sufficient to suggest that 1,1-DCE should be regulated as a carcinogen, since it is unlikely that environmental exposure would occur to the substance and a phorbol ester such as PMA.

Table V-17 contains a summary of the results of the several carcinogenicity studies described in detail above.

There are no reported data on whether cis- or trans-1,2-DCE is a chemical carcinogen.

Table V-17

Summary of Results from Carcinogenicity Studies with 1,1-DCE

Route	Species	Dose	Study Duration	Carcinogenic Response	Reference
Inhalation	Swiss Mice	10 ppm	98 weeks	negative	Maltoni, 1977; Maltoni et al., 1977
		25 ppm for 12 months	98 weeks	positive	
Inhalation	CD-1 Mice	55 ppm	52 weeks	negative	Lee et al., 1978
Not Reported	BALB/C Mice	Not Reported	Not Reported	negative	Fishbein, 1979 Report of Maltoni studies
	C56 BL Mice	Not Reported	Not Reported	negative	
	C_3H Mice	Not Reported	Not Reported	negative	
Inhalation	Rats (Sprague-Dawley)	10 ppm	98 weeks	negative	Maltoni, 1977; Maltoni et al., 1977
		25 ppm	98 weeks	negative	
		50 ppm	98 weeks	negative	
		100 ppm	98 weeks	positive	
		150 ppm	98 weeks	positive	
		12 months			
Inhalation	Rats (Sprague-Dawley)	75 ppm	lifetime	negative	Viola and Caputo, 1977
		200 ppm		negative	
		12 months			
Inhalation	Rats (Wistar)	75 ppm 200 ppm 12 months	lifetime	negative	Viola and Caputo, 1977
Inhalation	Rats (CD)	55 ppm	52 weeks	negative	Lee et al., 1978
Inhalation	Rats	25 ppm 75 ppm 18 months	104 weeks	negative	Rampy et al., 1977

(continued on next page)

Table V-17 (Continued)

Route	Species	Dose	Study Duration	Carcinogenic Response	Reference
Inhalation	Chinese Hamsters	25 ppm	74 weeks	negative	Maltoni, 1977; Maltoni et al., 1977
Oral (gavage)	Rats (BDIV)	50 mg/kg/day	120 weeks	negative	Ponomarkov and Tomatis, 1980
Oral (gavage)	Rats (Sprague-Dawley)	0.32 mg/kg/day 3.2 mg/kg/day 6.4 mg/kg/day 13 mg/kg/day	136 weeks	negative negative	Maltoni
Oral (drinking water)	Rats (Sprague-Dawley)	7-9 mg/kg/day 10-14 mg/kg/day 20-30 mg/kg/day	104 weeks	negative negative negative	Rampy et al., 1977 Quast et al., 1983
Oral (gavage)	Rats (F344)	1 mg/kg/day 5 mg/kg/day	104 weeks	negative	NTP, 1982
	Mice (B6C3F1)	1 mg/kg/day 5 mg/kg/day	104 weeks	negative	NTP, 1982
Subcutaneous	Swiss mice			inactive as whole mouse initiator	Van Duuren et al., 1979
		121 mg	single dose	active as initiator with phorbol myristate acetate	

VI. HEALTH EFFECTS IN HUMANS

A. Acute and Chronic Effects

CNS. At high concentrations, the DCEs possess anesthetic properties, as do other members of the chlorinated ethylene series. Although considerable research has been done on those compounds which were used as general anesthetics, little is known concerning the short- or long-term effects of DCEs on the CNS. The CNS depressant effect has been described from unpublished data (Irish, 1963). A concentration of 4000 ppm was estimated as sufficient to produce rapidly a state resembling drunkenness and was judged likely to result in unconsciousness if exposure were continued. A single report has been made associating sensory disturbance in the facial areas controlled by the trigeminal nerve with an accidental exposure to 1,1-DCE (Broser et al., 1970). Subsequent evaluation, however, suggested that the toxic agent was either mono- or dichloroacetylene, a contaminant of the 1,1-DCE (Henschler et al., 1970). No further information is available on the CNS effects of these compounds.

Teratogenicity/Mutagenicity. No studies addressing mutagenic or reproductive hazards among 1,1-DCE-exposed populations have been reported (Bahlman et al., 1979).

Carcinogenicity. There are no adequate data to permit an evaluation of the carcinogenic risk of 1,1-DCE to humans (Bahlman et al., 1979). One study reported no excessive cancer risk among 138 workers occupationally exposed to 1,1-DCE. However, methodological limitations of this study

(Ott et al., 1976) do not permit an adequate evaluation of the carcinogenic risk, since the number of individuals lost to follow-up in this study was high and the period of observation was relatively short. In a second study, mortality was examined among 629 workers occupationally exposed in a 1,1-DCE production and polymerization plant where there was also exposure to vinyl chloride and acrylonitrile. It was reported that 7 of the 35 deaths that occurred were from malignant tumors. This was not greater than the expected number. Two bronchial carcinomas occurred in persons aged 35 to 39, whereas 0.08 were expected. However, no information was given on smoking habits (Theiss et al., 1977).

Immunological Response. A study was made of the effect of 1,1-DCE on the ability of murine and human lymphocytes to respond to mitogenic agents, allogenic lymphocytes of the antigenic nature of 1,1-DCE itself (Thurman et al., 1978). 1,1-DCE was found to cause no change in the response of lymphocytes to various stimuli and to have very low toxicity to lymphocytes.

Other Adverse Effects. Reports of effects on workers exposed to 1,1-DCE in combination with other vinyl compounds include liver function abnormalities, headache, vision problems, dizziness, weakness, fatigue and neurological sensory disturbances (NIOSH, 1979).

B. Epidemiology

There have been no adequate epidemiological studies of the DCEs that have not also involved exposure to other compounds, e.g., vinyl chloride or acrylonitrile. The limited number of epidemiological investigations involving multiple compound exposures have been described above. These studies provide little evidence from which to define a human dose-response for the DCEs.

VII. MECHANISMS OF TOXICITY

The DCEs are readily absorbed and undergo rapid systemic distribution due to their lipid solubility and blood:gas partition coefficient. Accordingly, there is a fairly rapid equilibration throughout the body following exposure by any route of administration.

The DCEs, like other chlorinated hydrocarbons, have a depressant effect on the CNS which could lead to narcosis and, at high doses, ultimately cause death, probably due to respiratory depression. The exact neuronal mechanism of the CNS depression is unknown.

Although very little is known about the mechanism of toxicity of cis- and trans-1,2-DCE, there has been considerable work on the mechanism of toxicity of 1,1-DCE. Aside from its CNS depressant effect, which is probably due to 1,1-DCE *per se*, most of the acute and long-term toxic effects observed, e.g., hepatotoxicity, renal toxicity, mutagenicity and carcinogenicity, are probably due to the formation of toxic metabolites. For short-term inhalation exposures, mortality occurred in rats after the formation of 25 to 30 mg of metabolites/kg (Andersen et al., 1979b). Mice metabolize 1,1-DCE more rapidly than rats and there is a corresponding higher mortality resulting from a given dose with mice, presumably due to the formation of greater amounts of toxic metabolites (Short et al., 1977a; Maltoni, 1977; Jones and Hathway, 1978b).

The biotransformation of 1,1-DCE has been demonstrated to be a saturable process that follows Michaelis-Menten kinetics. At low doses, below the metabolic saturation point, the majority of an administered dose is metabolized to water-soluble products which are excreted via the kidney. However, when a large dose of 1,1-DCE are administered by any route and metabolism is saturated, larger amounts of untransformed 1,1-DCE are excreted via the lungs. There are also differences in the toxic effects caused by continual exposure to 1,1-DCE as compared to those caused by repeated intermittent exposures. Whereas adverse reactions including increased lethality were observed in several species following continual exposures to 1,1-DCE concentrations as low as 5 ppm, no toxic effects were observed following exposure for 8 hr/day, 5 days/week for 6 weeks to 100 ppm (Prendergast et al., 1967). The intermittent exposure regimen probably permitted elimination of 1,1-DCE and restoration of GSH levels between exposures. Similarly, at high exposure concentrations, the acute inhalation toxicity was related to the duration of the exposure, i.e., the total amount of toxic metabolite formed when biotransformation was proceeding at V_{max}, rather than to the ambient concentration (Andersen et al., 1979a). At low concentrations, it has been suggested that the rate of biotransformation of 1,1-DCE is limited by the blood flow to the liver. Since the rate at which an inhaled chemical is presented to the liver is related to pulmonary uptake, it would be expected that the smaller breathing volume (l/kg/hr) in man relative to the rat would decrease the relative amount of 1,1-DCE presented to the liver in man (Andersen et al., 1980a) and, presumably, formation of smaller amounts of toxic metabolite(s).

The metabolism of 1,1-DCE is generally hypothesized to proceed via oxidation of the parent compound by the MFO, following one of several pathways: reaction with GSH to produce a metabolite that undergoes renal excretion; reaction with macromolecules to produce covalently bound metabolites or rearrangement to form chloroacetyl chloride. This latter compound can either react with macromolecules or undergo hydrolysis to form chloroacetic acid, which reacts with GSH to form a series of water-soluble metabolites (see Figure III-2). It is generally believed that reaction of these metabolites, i.e., 1,1-DCE oxide, chloroacetyl chloride and chloroacetic acid, with macromolecules leads to hepatotoxicity, renal toxicity, mutagenicity and/or possibly carcinogenicity.

Since increased susceptibility to liver damage has been demonstrated when hepatic GSH concentration is decreased and conjugation with GSH is apparently a detoxication mechanism, the extent of hepatoxicity of 1,1-DCE appears to be related to the rate of formation of toxic metabolites. Supporting this theory is the fact that thyroidectomy, which increases hepatic GSH concentration, decreases hepatotoxicity (Szabo et al., 1977; Jaeger et al., 1977b). It has also been shown that there is an increase in 1,1-DCE metabolites covalently bound to liver macromolecules when the GSH levels are decreased.

A greater percentage of any administered dose of 1,1-DCE is metabolized in mice relative to rats; an effect attributed to the higher cytochrome P-450 activity of mice (Jones and Hathway, 1978b). This difference in biotransformation is reflected in a change in the ratio of the metabolites formed. In addition, the administration of 1,1-DCE has a greater toxic effect in mice (oral LD_{50} - 200 mg/kg) than in rats (oral LD_{50} - 1500 mg/kg). The difference in the LD_{50} may represent the relative ability of the two species to form toxic metabolites from 1,1-DCE. It has also been shown that there are much higher levels of covalently bound 1,1-DCE metabolites in both liver and kidneys of mice than of rats.

The liver damage characteristically caused by exposure to most chlorinated hydrocarbons is injury to the endoplasmic reticulum. Since 1,1-DCE causes nuclear changes, mitochondrial swelling and rupture of outer mitochondrial membranes, there appear to be basic differences in their mechanisms of toxicity. It has been suggested that the monochlorocitric acid formed from chloroacetic acid could inhibit mitochondrial function and be the molecular basis for hepatic injury (Jaeger, 1977a).

Moore (1980) also has shown that the microsomal ATP-dependent calcium pump can be inhibited by 1,1-DCE administration and that 1,1-DCE was more effective than chloroform and almost as effective as carbon tetrachloride (CCl_4) in microsomes isolated from male adult Sprague-Dawley rats. Further studies (Moore, 1982) showed that calcium pump activity could be inhibited by

45% within 20 min after a dose of 1.5 ml 1,1-DCE/kg in rats. The only other measured parameter which declined as rapidly was GSH concentration. However, administration of diethylmaleate also produced GSH depletion, but did not cause calcium pump inhibition or release of microsomal calcium. The inactivation of the microsomal ATP-dependent calcium pump by 1,1-DCE metabolites also has been demonstrated *in vitro* (Ray and Moore, 1982). These studies suggest that the microsomal calcium pump may be a critical target for 1,1-DCE alkylation and that disruption of cellular calcium homeostasis may be important in the toxicity of this chemical. However, it must be remembered that 1,1-DCE and CCl_4 cause different types of hepatic injury, so the data on the inhibition of the calcium pump activity by 1,1-DCE and CCl_4 must be interpreted with caution.

The renal damage caused by 1,1-DCE is characterized by vacuolization, tubular dilatation and necrosis. There is a considerable amount of covalent binding of 1,1-DCE metabolites in kidneys in both mice and rats. Mice have been shown to be more susceptible to kidney damage from 1,1-DCE than rats.

The mutagenic potential of the DCEs has been studied. None of the isomers was mutagenic in bacterial systems without microsomal activation. However, in the presence of microsomal fractions from liver, kidney and lung from mice and rats, and from human liver, 1,1-DCE was shown to be mutagenic in *S. typhimurium* and *E. coli* (Jones and Hathway, 1978c). Pretreatment of animals with microsomal enzyme modifiers affected the mutagenicity of 1,1-DCE. These data have been interpreted that the mutagenicity of 1,1-DCE is due to the formation of an unsymmetrical, highly reactive metabolite which binds to the bacterial DNA (Henschler et al., 1976; Henschler, 1977; Henschler and Bonse, 1977). In contrast, metabolism of cis- and trans-1,2-DCE produces symmetrical metabolies which are more stable and do not react with DNA. However, the finding of increased bacterial mutation rates by 1,1-DCE has not been confirmed using mammalian systems, as both mice and rats exposed to 1,1-DCE failed to produce dominant lethal mutations.

Several studies have been conducted to investigate the carcinogenic potential of 1,1-DCE. Using several routes of administration to Ha:ICR Swiss mice, it was shown that 1,1-DCE was inactive as a whole mouse skin carcinogen and inactive by subcutaneous injection, but was active as a skin tumor initiator in a two-stage carcinogenesis assay using PMA as a promoter (Van Duuren et al., 1979). In one carcinogenicity study, mice (Swiss, BALB/C, C56BL, and C_3H strains) rats (Sprague-Dawley) and hamsters were exposed to 1,1-DCE. At exposure to 10 ppm, there was no increased incidence of any tumor in any species. Exposure to 25 ppm of 1,1-DCE caused a statistically significant increase in kidney adenocarcinomas in Swiss mice, almost exclusively in the males (24/150 in males compared to 1/150 in females). Also, a statistically significant increase in mammary adenocarcinomas was found in Swiss mice at 25 ppm and in Sprague-Dawley rats at 100 and

150 ppm. No increase in kidney adenocarcinomas was found in Sprague-Dawley rats at exposures up to 200 ppm. Additionally, it has been reported that other studies by Maltoni found no statistically significant increased incidence of any tumor in BALB/c, C56BL or C_3H mice (Fishbein, 1979), or in hamsters (Maltoni, 1977; Maltoni et al., 1977).

A study using CD-1 mice and CD rats exposed to 55 ppm of 1,1-DCE found no statistically significant increase in incidence of kidney adenocarcinoma in mice or rats, while 2 rats developed hemangiosarcomas which were considered to be caused by 1,1-DCE (Lee et al., 1978). Three additional carcinogenicity studies conducted with rats (Sprague-Dawley, Wistar and BDIV strains) provided no unequivocal evidence for carcinogenicity of 1,1-DCE in rats (Viola and Caputo, 1977; Rampy et al., 1977; Ponomarkov and Tomatis, 1980). Further studies on the carcinogenic potential of 1,1-DCE in mice and rats sponsored by NTP have been completed which suggest that, at least at the doses used, 1,1-DCE is not carcinogenic by gavage.

In summary, the carcinogenic potential of 1,1-DCE has been shown to be quite different from that of vinyl chloride. Vinyl chloride has been shown to produce hepatic angiosarcomas, sebacious carcinomas, cutaneous skin tumors and forestomach papillomas in rats, mice and hamsters as well as mammary carcinomas in both rats and mice. Additionally, vinyl chloride has been found to cause liver angiosarcoma in humans. For 1,1-DCE, the reports of carcinogenicity are conflicting and indicate sex, species and strain and route of exposure differences. In mice, the most pronounced increases in tumor incidence caused by 1,1-DCE were kidney adenocarcinoma and mammary gland adenocarcinoma in Swiss mice. However, kidney adenocarcinomas were observed almost exclusively in male Swiss mice, and neither tumor type was observed in four other strains of mice. In rats, an increase in mammary gland adenocarcinomas was found in Sprague-Dawley rats in one study, but was not found in a second study using the same strain or in studies using two other strains. Additionally, 1,1-DCE was inactive as a carcinogen in hamsters.

It has been suggested that development of kidney adenocarcinomas in mice is due to the increased rate of biotransformation of 1,1-DCE in mice, which produces a higher level of reactive intermediates that can subsequently react with macromolecules, e.g., DNA (Maltoni, 1977; Hathway, 1977; Henschler and Bonse, 1977). A study has been made of the potential of 1,1-DCE to cause DNA alkylation, DNA repair and DNA replication in the liver and kidneys of mice and rats, and these results were compared to those obtained using dimethylnitrosamine (DMN), a potent carcinogen (Reitz et al., 1980). Tumorigenic doses of DMN produced relatively little tissue damage, but caused a high degree of DNA alkylation and DNA repair. These data were interpreted as suggesting that tumors observed in mice exposed to 1,1-DCE arise primarily through epigenetic mechanisms, i.e., effects of the chemical on nongenetic components.

Multiple Chemical Exposure; Potential for Interaction.

Jackson et al. (1982) investigated the interaction of 1,1-DCE with 1,2-dichloroethane (1,2-DCEthane). The compounds were administered via inhalation alone and together in several combinations. Their potential for acute hepatotoxicity and nephrotoxicity was assessed.

Male Sprague-Dawley rats were fasted overnight prior to exposure. Each was subjected in single 4 hr exposures to 200, 250 or 300 ppm 1,1-DCE alone, to 1,400, 1,600, 1,800 or 2,100 ppm 1,2-DCEthane alone or to combinations of 1,1-DCE and 1,2-DCEthane in the following ratios: 200/1,200, 300/1,800 or 400/2,400 (see Table VII-1 for doses and animals/group). The dose combinations were chosen to reflect roughly equivalent potencies with respect to each compound's nephrotoxic effect.

Twenty hr after termination of exposure, the animals were sacrificed and blood collected. Nephrotoxicity was measured by kidney to body weight ratios, BUN and creatinine levels, while SDH activity was used as an indicator of hepatotoxicity.

1,1-DCE, at all doses, caused very large increases in SDH levels, while changes after 1,2-DCEthane exposure were much less (Table VII-1). The statistical significance of the effects, alone or in combination, were not reported. However, it appears that exposures to 1,1-DCE and 1,2-DCEthane elicited responses that were similar to exposures to 1,1-DCE alone.

Table VII-1

Measure of Hepatotoxicity to Rats from Exposure to 1,1-DCE and 1,2-DCEthane[a]

Treatment[b]	N[c]	serum SDH[d]
Control	10	1.8 ± 1.0
1,1-DCE		
200 ppm	4	94.0 ± 9.1
250 ppm	4	832.0 ± 158.1
300 ppm	4	706.7 ± 133.8
1,2-DCEthane		
1400 ppm	4	1.4 ± 1.4
1600 ppm	6	9.5 ± 1.4
1800 ppm	4	---
2100 ppm	6	17.0 ± 3.0
2400 ppm	6	33.2 ± 5.3
1,1-DCE/1,2-DCEthane		
200/1200	4	203.8 ± 110.1
300/1800	5	745.4 ± 116.2
400/2400	5	824.3 ± 151.4

---

[a] From Jackson et al., 1982.

[b] Exposure concentration of 1,1-DCE and/or 1,2-DCEthane for 4 hours via inhalation.

[c] number of animals, pooled controls.

[d] serum sorbitol dehydrogenase ± S.E. measured at 30°C in mg/dl.

An antagonistic effect on the kidney was demonstrated (see Table VII-2). When animals were exposed either to 300 ppm 1,1-DCE or 1800 1,2-DCEthane for 4 hr, significant increases occurred in the 3 parameters measuring nephrotoxicity. When animals were exposed to the same levels of each substance in combination, each parameter was decreased significantly from the levels observed when each chemical was administered separately ($P < 0.05$). A similar antagonism also was reported after exposure to a mixture of 200 ppm 1,1-DCE and 1200 ppm 1,2-DCEthane, although this mixture had no nephrotoxic effect (data not shown). With simultaneous exposure to 400 ppm 1,1-DCE and 2400 ppm 1,2-DCEthane, fewer rats died than would be expected based upon the LD_{50} of 1,1-DCE alone. The mean values for nephrotoxicity of this mixture was equal to 2400 ppm 1,1-DCE alone (data not presented).

Since each compound shares common routes of metabolism in the liver, and, presumably, also, in the kidney, the authors proposed that this antagonism might arise from competition for metabolic pathways. Thus, at these exposure levels, either chemical could be inhibiting the activation or detoxication of the other. It would be important to establish whether or not this antagonistic interaction would occur at low levels of exposure, particularly in the range of occurrence in drinking water.

More recent studies have focused on the interaction of other chemicals with 1,1-DCE. As in the case with several halogenated alkanes, low doses of acetone can potentiate the

Table VII-2

Antagonistic Effect of a Combined 1,1-DCE and 1,2-DCEthane Exposure on Nephrotoxicity[a]

Treatment[b]	N[c]	Kidney/body weight[d] (x ± S.E.)	Serum urea nitrogen[e] (x ± S.E.)	Serum creatinine[f] (x ± S.E.)
Control	20	0.89 ± 0.07	8.25 ± 0.47	0.64 ± 0.01
300 ppm 1,1-DCE	4	1.66 ± 0.12	40.93 ± 11.30	1.79 ± 0.34
1800 ppm 1,2-DCEthane	4	1.57 ± 0.13	65.39 ± 4.87	4.51 ± 0.17
300 ppm 1,1-DCE + 1800 ppm 1,2-DCEthane	5	1.12 ± 0.10[g]	22.64 ± 7.45[g]	1.55 ± 0.55[g]

---

[a] Jackson et al., 1982.

[b] Four-hour inhalation exposures, controls pooled from several experiments.

[c] number of animals in group.

[d] g kidney/100g body weight.

[e] mg urea nitrogen/10 ml serum.

[f] mg creatinine/100 ml serum.

[g] values significantly less than values for 300 ppm 1,1-DCE or 1800 ppm 1,2-DCEthane alone ($P < 0.05$).

toxicity of 1,1-DCE (Hewitt and Plaa, 1983). This study involved male Sprague-Dawley rats (150 to 300 g) and 50 mg/kg doses of 1,1-DCE (po in oil). After 24 hr, serum enzymes were from 2.5 to 10 times higher in animals treated with 5 or 10 mmol/kg acetone plus 1,1-DCE in comparison to animals receiving 1,1-DCE only. Higher doses of acetone (15 to 30 mmol/kg) did not produce this effect. 1,1-DCE administration can result in increased endogenous acetone production (Filser and Bolt, 1980), but it is not known if this could have potentiated 1,1-DCE toxicity.

Both diethyldithiocarbamate and carbon disulfide blocked the renal damage of 1,1-DCE in male ddY mice (Masuda and Nakayama, 1983). This protection is thought to be due to inhibition of enzymes which activate 1,1-DCE. These authors also reported a hypothermic effect of 1,1-DCE (up to -10°C). Diethyldithiocarbamate blocked the hypothermic response caused by administration of 1,1-DCE, but did not block the hypothermia which resulted from the administration of chloroacetyl chloride or chloroacetic acid, known metabolites of 1,1-DCE. This is consistent with the view that by 1,1-DCE must be metabolized to cause hypothermia.

Several efforts have been made to examine the influence of dietary factors on 1,1-DCE metabolism and toxicity. Nakajima et al, (1982) varied protein, carbohydrate and fat components in diets fed to adult male Wistar rats and concluded that only low carbohydrate diets showed significant effects on the metabolism of 1,1-DCE. In this study, liver microsomes were examined for their ability to deplete 1,1-DCE from the atmosphere. Rats fed a low carbohydrate diet showed a 2-fold increase in this rate. In a subsequent study (Sato et al., 1983), the effects of the low carbohydrate diet in this model were retested and there was a 1.5-fold increase in the *in vitro* rate of 1,1-DCE uptake. In addition, administration of a high level of ethanol to the rats for 3 weeks produced a 2- to 4-fold increase in the rate of 1,1-DCE uptake. On the other hand, studies by Siegers et al. (1983) indicated that treatment of male Wistar rats with ethanol for 7 days did not influence the *in vivo* uptake of 1,1-DCE, but increased the hepatotoxicity of a 125 mg/kg dose (po in olive oil) of 1,1-DCE as judged by release of serum enzymes. Pretreatment of rats with ethanol for 24 hours prior to 1,1-DCE administration had no effect on hepatotoxicity, while simultaneous administration of ethanol decreased 1,1-DCE toxicity. Siegers et al. (1983) also reported that dithiocarb and (+)catechin block both the hepatotoxicity and acute toxicity of 1,1-DCE in rats.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an separate assessments of noncarcinogenic and carcinogenic effects. Those chemicals which produce noncarcinogenic effects are believed to have a threshold dose below which no adverse effects occur. Carcinogens are assumed to act without a threshold.

Quantification of Noncarcinogenic Effects

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), formerly called Acceptable Daily Intake (ADI) is calculated. The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects, even if exposure occurs over a lifetime. The RfD is derived from a No-Observed-Adverse-Effect-Level (NOAEL), or Lowest-Observed-Adverse-Effect-Level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s). The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{(NOAEL or LOAEL)}}{\text{Uncertainty Factor(s)}} = \underline{\qquad} \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based on professional judgment, taking the entire data base of toxicological effects for the chemical into consideration. In order to ensure that uncertainty factors are slected and applied in a consistent manner, the Office of Drinking Water (ODW) has modified the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

- An uncertainty factor of 10 is generally used when good acute or chronic human exposure data identifying a

NOAEL are available and are supported by good acute or chronic toxicity data in other species.

- An uncertainty factor of 100 is generally used 1) when good acute or chronic toxicity data identifying a NOAEL are available for one or more animal species (and human data are not available), or 2) when good acute or chronic toxicity data identifying a LOAEL in humans are available.
- An uncertainty factor of up to 1,000 is generally used 1) when limited or incomplete acute or chronic toxicity data are available, or 2) when good acute or chronic toxicity data identify a LOAEL, but not a NOAEL for one or more animal species.

The uncertainty factor used for a specific risk assessment is based principally on scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving a RfD, the significance of the adverse effect and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL is a medium specific (i.e., drinking water) lifetime exposure, assuming a 100% relative source contribution from that medium, at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL value is intended to provide the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived at follows:

$$\text{DWEL} + \frac{(\text{RfD}) \times (\text{Body Weight in kg})}{\text{Drinking Water Volume in L/day}} = \underline{\hspace{2em}}\text{mg/L}$$

where:

Body weight = assumed to be 70 kg for an adult

Drinking water volume = assumed to be 2 liters per day for an adult

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (One-day, Ten-day, and Longer-term) are determined. The HA values are used as an informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using a similar equation as the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{bw})}{(\text{UF}) \times (\underline{\hspace{2em}}\text{L/day})} = \underline{\hspace{2em}}\text{mg/L}$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. One-day HA for a 10-kg child ingesting 1 L water per day.
2. Ten-day HA for a 10-kg child ingesting 1 L water per day.
3. Longer-term HA for a 10-kg child ingesting 1 L water per day.
4. Longer-term HA for a 70-kg adult ingesting 2 L water per day.

The One-day HA calculated for a 10-kg child assumes a single acute exposure to the chemical and is generally derived from a study of less than seven days duration. The Ten-day HA assumes a limited exposure period of one to two weeks and is generally derived from a study of less than a 30-day duration. The Longer-term HAs are derived for both the 10-kg child and a 70-kg adult and assumes an exposure period of approximately seven years (or 10% of an individual's lifetime). The Longer-term HAs are generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

Quantification of Carcinogenic Effects

It is not always simple to decide whether a chemical is a carcinogen or not, since available studies may be limited, inadequate or inconsistent. The EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

- Group A: Known Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal relationship between exposure to the chemical and human cancer.
- Group B: Probable Human Carcinogen. Adequate evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
- Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
- Group D: Not classified. Inadequate evidence of carcinogenicity in animals.
- Group E: No evidence of carcinogenicity. No evidence of carcinogenicity in adequate tests in two different animal species or in both animal and epidemiology studies.

If toxicological evidence leads to the classification of the contaminant as a known or probable human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these estimates usually comes from lifetime exposure studies in animals. In order to predict the risk for humans from animal data, animal doses must be converted to an equivalent human dose. This conversion includes correction for noncontinuous exposure, less than lifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is two liters of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure via ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any others. Because each model is based upon differing assumptions, the estimates which are derived for each model can differ by several orders of magnitude.

The scientific database used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exists, such as the imcomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure on the internal targets in experimental animals or humans. Dose response data usually are available only for high levels of exposure, not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

A. Noncarcinogenic Effects

The principal toxic effects of the DCEs following acute and longer-term exposures are upon the liver and kidney. In addition, like other members of the chlorinated ethylene series, they also possess general anesthetic and narcotic properties. Available data suggest that the CNS effects occur at exposure levels near or above those at which the liver and kidney effects are seen, even with acute exposures.

Acute toxicity, as measured by the LD_{50}, has been reported in several studies (Jenkins et al., 1972; Andersen and Jenkins, 1977; Freundt et al., 1977; Andersen et al., 1979a; 1977; Jones and Hathway, 1978b; NIOSH, 1978; Ponomarkov and Tomatis, 1980) and are summarized in Table V-1.

The wide range in lethality observed for 1,1-DCE is dependent upon a number of factors: 1) nutritional status - fasted animals are more sensitive than fed animals; 2) age - younger, smaller animals are more sensitive than older, larger ones; 3) species - exposure to the same inhalation dose results in more severe effects in mice than in rats; and 4) sex - with repeated dosing, male mice are more sensitive than females.

A number of studies on 1,1-DCE have been reported which are of sufficient length (subchronic or chronic exposure) to be useful in the development of Longer-term Health Advisories (HAs), a DWEL or Lifetime HAs. These studies describe good dose-response data which permit identification of No-Observed-Adverse-Effect-Levels (NOAELs) or Lowest-Observed-Adverse-Effect-Levels (LOAELS). In several of these studies, the animals were exposed to the substance orally, either by gavage or in drinking water. Equivalent studies for cis- and trans-1,2-DCEs are limited. However, the available information suggests that although animals exposed to each of the DCEs will have a greater amount of cis- and/or trans-1,2-DCE isomer in their bodies at equilibrium than of 1,1-DCE. The non-carcinogenic toxicity induced by the 1,2- isomers appears to be less severe than that induced by an equivalent dose of 1,1-DCE basis (Jenkins et al., 1972; Filser and Bolt, 1979). Since the end-points of non-carcinogenic toxicity to all three DCEs are similar, it is suggested that the HA numbers developed for 1,1-DCE be applied to cis-1,2-DCE and trans-1,2-DCE, when there are no other available data. This would provide an added margin of safety and is consistent with the regulatory philosophy that seeks to avoid underestimating the potential risk. In addition, it would provide a basis for the development of DWELs and Maximum Contaminant Level Goals (MCLGs) for the 1,2-DCE isomers. It is always preferred that HAs and RMCLs be based upon data generated in studies of the specific compounds, but the appropriate data for the 1,2- isomers do not exist, and resolution of the contamination of drinking water with the 1,2-DCE isomers of is required. Therefore, the Ten-day, the Longer-term and Lifetime HAs developed for 1,1-DCE will also be applied to cis-1,2-DCE and the 1,1-DCE Lifetime HA to trans-1,2-DCE.

B. Quantification of Noncarcinogenic Effects

1. One-day Health Advisories

1,1-Dichloroethylene

Jenkins et al. (1972) reported that single oral doses of 1,1-DCE, at concentrations of 100, 300 and 500 mg/kg, in corn oil to fasted rats caused significant dose-dependent alterations in the plasma levels of glucose-6-phosphatase, SAP and SGPT. However, this study is not considered to be appropriate, since subsequent studies have shown that fasting (Jaeger et al., 1974; Andersen and Jenkins, 1977) and administering 1,1-DCE in corn oil (Chieco et al., 1981) potentiate the hepatotoxic effects of 1,1-DCE. Chieco and coworkers (1981) have reported that when 200 mg/kg of 1,1-DCE was given in an aqueous solution of 0.5% Tween 80, the chemical caused only a slight increase in SGPT, but not SGOT. In addition, the pathological changes observed in the liver were limited to a few scattered microfoci of necrosis. Accordingly, the 200 mg/kg is taken to be the LOAEL.

The One-day HA for the 10 kg child is calculated as follows:

$$\text{One-day HA} = \frac{(200\text{ mg/kg/day})\ (10\text{ kg})}{(1{,}000)\ (1\text{ L/day})} = 2.0\text{ mg/L }(2{,}000\text{ ug/L})$$

where:

200 mg/kg/day = LOAEL, based on hepatic effects.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

cis-1,2-Dichloroethylene

There are few animal studies which provide dose-response data on the effects of cis-1,2-DCE (Irish, 1963; Jenkins et al., 1972; Freundt and Macholz, 1978). Only the study by Jenkins et al. provides sufficient information from which a One-day HA can be calculated. They monitored levels of liver glucose-6-phosphatase, liver alkaline phosphatase, liver tyrosine transaminase, SAP and SGPT and observed that a single, oral dose of 400 mg/kg to the rat produced a significant change only in liver alkaline phosphatase. This slight degree of liver involvement is not felt to be life-threatening and appears to be reversible after exposure has been discontinued.

However, subsequent research has revealed that two experimental conditions (18-hr fast and use of a corn oil vehicle) used by Jenkins et al. (1972) potentiated the hepatotoxicity of 1,1-DCE, a close structural analog of cis-1,2-DCE. For example, fasting (Andersen and Jenkins, 1977; Jaeger et al., 1977a) and the use of corn oil as a vehicle (Chieco et al., 1981) increased the toxicity [the LOAEL was doubled from 100 to 200 mg/kg by not fasting or using corn oil; Chieco et al. (1981)]. Although it is considered likely that corn oil and fasting could alter the toxicity of cis-1,2-DCE, there are no specific data and the LOAEL of 400 reported by Jenkins et al. (1972) will be used for the one-day calculations.

The One-day Health Advisory for the 10 kg child is calculated as follows:

$$\text{One-day HA} = \frac{(400\ \text{mg/kg/day})\ (10\ \text{kg})}{(1{,}000)\ (1\ \text{L/day})} = 4.0\ \text{mg/L}\ (4{,}000\ \text{ug/L})$$

where:

400 mg/kg/day = LOAEL, based on an increase in liver alkaline phosphatase activity.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

trans-1,2-Dichloroethylene

Freundt et al. (1977) reported the effects of trans-1,2-DCE after inhalation by mature female Wistar rats (180 to 200 g) at 200 ppm (800 mg/m^3, the currently established TLV/MAC in many countries) or at 1000 or 3000 ppm (4000 or 12000 mg/m^3, respectively). A brief (8 hr) or prolonged exposure (8 hr/day, 5 days/week for 1, 2, 8 or 16 weeks) at 200 ppm resulted in such adverse effects as an increased incidence of slight degeneration of the liver lobule and lipid accumulation by the Kupffer cells. This response occurred in only 1 of the 6 rats treated for 8 hr at this dose. Two of 6 rats showed slight changes after 1 week of exposure; 3 of 6 rats exhibited slight changes during the 2 week exposure. Damage became more evident in a higher percentage of the animals as the length of exposure increased to 8 or 16 weeks. At all exposure levels, the appearance of pulmonary capillary hyperemia and distention of the alveolar septum was increased over that observed in the controls. At 8 and 16 weeks of exposure, severe pneumonic infiltration was observed in 3 of the 6 treated rats; this phenomenon did not occur in any of the controls.

At each of the 2 higher levels of single-day exposure, liver and pulmonary effects similar to those observed at 200 ppm were seen in 2 of 6 treated at each dose. At these higher levels, fibrous swelling and hyperemia of cardiac muscle also occurred in 4 of 6 rats treated at each exposure level. This effect persisted for at least 14 hr post-exposure, although the liver effects appeared to be reversing by that time.

At all doses and durations of exposure, there was no evidence of abnormal pathology involving the kidney, spleen, brain, striated muscle (quadriceps) or peripheral nerve, nor were there signs of CNS depression.

A number of biochemical and hematological parameters also were tested. No changes in serum cholesterol, albumin, uric acid, BUN, glucose, SAP, SGOT or SGPT were observed after the single 8 hr exposure at 200 ppm. Exposure at 1,000 ppm for 8 hr resulted in significant reductions in serum albumin, BUN and SAP. Eight hr exposures at both 200 and 1,000 ppm caused a significant decrease in the number of leucocytes. Since leucocyte count may be affected by external stimuli [physical exertion, stress and food intake (Lentner, 1984)], the number of leucocytes in this study (2.5×10^3) appears to be lower than normal for rats [6 to $17 \times 10^3/mm^3$ (Harkness and Agner, 1983)] and there is no dose-response noted in the 200 and 1,000 ppm groups, it is difficult to evaluate the reported decrease in leucocytes. Accordingly, this parameter will not be used in setting the NOAEL. Clinico-chemical parameters were not studied at the 3,000 ppm exposure level.

A NOAEL of 200 ppm over a single 8 hr exposure was identified for trans-1,2-DCE based upon the normal biochemical parameters and on the slight liver effects in only 1 of 6 rats.

The One-day Health Advisory for the 10 kg child is calculated as follows:

Step 1: Determination of total absorbed dose (TAD)

$$\text{TAD} = \frac{200 \times 3.97\ (\text{mg/m}^3) \times 0.006\ (\text{m}^3/\text{hr}) \times 8}{(0.19\ \text{kg})} = 200\ \text{mg/kg}$$

where:

200 x 3.97 (mg/m^3) = total absorbed dose converted from ppm to mg/m^3.

0.006 = conversion factor to obtain m^3/hr for 190 g rats, i.e., 100 mL/min x 60 min/hr divided by 1,000,000 (ml to m^3).

8 = duration of exposure in hours.

0.19 = average weight in kg of exposed rats.

Step 2: Determination of One-day Health Advisory

$$\text{One-day HA} = \frac{(200\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 20.0\ \text{mg/kg}\ (20{,}000\ \text{ug/L})$$

where:

200 mg/kg/day = total absorbed dose.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisories

1,1-Dichloroethylene

Appropriate studies for the calculation of a Ten-day HA for 1,1-DCE are not available. However, evaluation of all toxicological data for 1,1-DCE suggests that the Longer-term HA for the 10-kg child would provide sufficient protection over a ten-day period as well. Thus, the Ten-day HA is 1,000 ug/L.

cis-1,2-Dichloroethylene

Adequate studies for the calculation of a Ten-day Health Advisory are not available. Evaluation of the toxicological data on cis-1,2-dichloroethylene suggests that the Longer-term Health Advisory of 3 mg/L should provide adequate protection over a 10-day exposure period.

trans-1,2-Dichloroethylene

The data of Barnes et al. (1985) are appropriate for calculation of the Ten-day HA. trans-1,2-Dichloroethylene was given by gavage in a 1:9 (v/v) mixture of emulphor and distilled water at levels of 21 and 210 mg/kg to male mice for 14 days. Neither dose had any effect on body or organ wet weight or on organ to body weight ratio. In addition, these doses did not affect LDH, SGPT or BUN. However, at 210 mg/kg, fibrinogen levels and prothrombin times were significantly decreased. From these data, a NOAEL of 21 mg/kg/day was identified.

The Ten-day HA for the 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(21\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 2\ \text{mg/kg}\ (2{,}000\ \text{ug/L})$$

where:

21 mg/kg/day = NOAEL based on normal hematology values.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisories

1,1-Dichloroethylene

A Longer-term HA can be calculated from a 90 day subchronic study in which rats of both sexes were given 1,1-DCE at concentrations of 0, 50, 100 or 200 ppm (0 to 25.6 mg/kg bw/day) in their drinking water (Rampy et al., 1977). Except for a decreased kidney:body weight ratio in males at the low dose, there were no statistically significant differences in organ weights or in organ:body weight ratios at the termination of the study. The only abnormal histopathology noted was an increased cytoplasmic vacuolization of hepatocytes in the livers of both sexes exposed to the highest dose. A NOAEL of 100 ppm (10 to 12.6 mg/kg) was identified.

A Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(10\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 1.0\ \text{mg/L}\ (1{,}000\ \text{ug/L})$$

where:

10 mg/kg/day = NOAEL, based on absence of liver effects.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

A Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(10\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 3.5\ \text{mg/L}\ (3{,}500\ \text{ug/L})$$

where:

all factors are the same except,

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

cis-1,2-Dichloroethylene

McCauley et al. (1990) gave cis-1,2-dichloroethylene in corn oil to Sprague-Dawley rats by gavage at doses of 0, 32, 97, 291 or 872 mg/kg/day for 90 days. In males a decreased hematocrit was observed at a dose of 97 mg/kg/day or greater. Based on normal hematocrit values, a NOAEL of 32 mg/kg/day was identified for cis-1,2-dichloroethylene.

The Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(32\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 3.2\ \text{mg/L (rounded to } 3{,}000\ \text{ug/L)}$$

where:

32 mg/kg/day = NOAEL based on the absence of hematologic effects.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(32\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 11.2\ \text{mg/L (rounded to } 11{,}000\ \text{ug/L)}$$

where:

32 mg/kg/day = NOAEL based on the absence of hematologic effects.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

trans-1,2-Dichloroethylene

Barnes et al. (1985) administered trans-1,2-DCE to CD-1 mice in their drinking water for 90 days at levels of 17, 175 or 387 mg/kg/day for males and 23, 224 or 452 mg/kg/day for females. They found that, in males, serum alkaline phosphatase was significantly elevated at the 175 and 387 mg/kg/day doses. In females, the thymus weight, calculated as % of body weight, was significantly decreased at the top two doses.

Based on the normal serum chemistry values in male mice, a NOAEL of 17 mg/kg/day was identified for trans-1,2-DCE.

A Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(17\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 2\ \text{mg/L}\ (2{,}000\ \text{ug/L})$$

where:

17 mg/kg/day = NOAEL based on normal serum chemistry values.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

A Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(17\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 6\ \text{mg/L}\ (6{,}000\ \text{ug/L})$$

where:

17 mg/kg/day = NOAEL based on normal serum chemistry values.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

4. Reference Dose and Drinking Water Equivalent Level

1,1-Dichloroethylene

The RfD and DWEL for 1,1-DCE can be calculated from the 2 year chronic study in rats (Quast et al., 1983). 1,1-DCE, at concentrations of 0, 50, 100 or 200 ppm (0 to 20 mg/kg/day) in drinking water, was administered to animals of both sexes. No consistent treatment-related changes were observed in any parameter measured. The only abnormal histopathology observed was mid-zonal fatty accumulation in the livers of both sexes receiving the highest dose. No liver degeneration was noted. A LOAEL of 100 ppm (10 mg/kg) was identified, based upon a trend towards increased fatty deposition in the liver.

Using this study the DWEL is derived as follows:

Step 1: Determination of RfD

$$\text{RfD} = \frac{(10\text{ mg/kg/day})}{(1{,}000)} = 0.01\text{ mg/kg/day}$$

where:

10 mg/kg/day = LOAEL for hepatic effects.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 2: Determination of DWEL

$$\text{DWEL} = \frac{(0.01\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.4\ \text{mg/L}\ (400\ \text{ug/L})$$

where:

0.01 mg/kg/day = RfD
70 kg = assumed body weight of an adult.
2 L/day = assumed daily water consumption of an adult.

cis-1,2-Dichloroethylene

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Lifetime toxicity data for cis-1,2-dichloroethylene do not exist. Accordingly, the 90-day study of McCauley et al. (1990) was considered for setting the Lifetime HA.

cis-1,2-Dichloroethylene was administered in corn oil to male and female Sprague-Dawley rats (20/sex/dose) for 3 months at doses of 0, 32, 97, 291 or 872 mg/kg/day. At doses of 97 mg/kg/day, administration of cis-1,2-dichloroethylene caused dose-dependent decreases in the hematocrit of male rats. A similar effect occurred in females starting at 291 mg/kg/day. A NOAEL of 32 mg/kg/day in male rats was identified.

A Drinking Water Equivalent Level (DWEL) and Lifetime HA for the 70-kg adult are calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(32\ \text{mg/kg/day})}{(3{,}000)} = 0.01\ \text{mg/kg/day}$$

where:

32 mg/kg/day = LOAEL based on absence of hematological effects.

3,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study with a less than adequate database.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.01 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.35 \text{ mg/L } (350 \text{ ug/L})$$

where:

0.01 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

trans-1,2-Dichloroethylene

Lifetime toxicity data for trans-1,2-DCE do not exist. Accordingly, the 90-day studies of Barnes et al. (1985) and Hayes et al. (1987) were considered for setting the Lifetime HA. Since the Barnes et al. (1985) study indicated that the mouse was more sensitive to this chemical than was the rat, the mouse data were used in calculating the Lifetime HA.

trans-1,2-Dichloroethylene was administered to CD-1 mice in their drinking water at doses of 17, 175 or 387 for males and 23, 224 or 452 mg/kg/day for females. In males, there were significant increases in serum alkaline phosphatase at 175 and 387 mg/kg/day, while in female mice, the thymus weight, calculated as % body weight, was decreased at the top two doses. A NOAEL of 17 mg/kg/day in male mice was identified based on normal serum chemistry values in male mice.

A Drinking Water Equivalent Level (DWEL) and Lifetime HA for a 70-kg adult are calculated as follows:

Step 1: Determination of RfD

$$\text{RfD} = \frac{(17 \text{ mg/kg/day})}{(1{,}000)} = 0.02 \text{ mg/kg/day}$$

where:

17 mg/kg/day = NOAEL based on normal serum chemistry values.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from a less-than-lifetime animal study.

Step 2: Determination of DWEL

$$\text{DWEL} = \frac{(0.017\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.6\ \text{mg/L}\ (600\ \text{ug/L})$$

where:

0.17 mg/kg/day = RfD

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

C. Carcinogenic Effects

1,1-Dichloroethylene. The carcinogenic potential of 1,1-DCE has been investigated in several species via various routes of exposure. The results of most of the studies fail to support a significant, treatment-related increase in tumor incidence following exposure to 1,1-DCE (Table VIII-1). In no oral exposure study, either by gavage or in drinking water, was there a significant tumor response. However, in some of the inhalation studies, there were significant increases in tumor incidences. In addition, 1,1-DCE was active as an initiator by subcutaneous injection, when combined with PMA as the promoter (Van Duuren et al., 1979).

Assessment of the carcinogenic potential of 1,1-DCE is complicated further by the fact that the positive data developed by Maltoni et al. (1985) are not absolutely conclusive.

TABLE VIII-1

Summary of Results from Carcinogenicity Studies with 1,1-DCE

Route	Species	Dose	Study Duration	Carcinogenic Response	Reference
Inhalation	Swiss Mice	10 ppm 25 ppm for 12 months	98 weeks 98 weeks	negative positive	Maltoni, 1977; Maltoni et al., 1977
Inhalation	CD-1 Mice	55 ppm	52 weeks	negative	Lee et al., 1978
Not Reported	RALB/C Mice C56 BL Mice C_3H Mice	Not Reported Not Reported Not Reported	Not Reported Not Reported Not Reported	negative negative negative	Fishbein, 1979 Report of Maltoni studies
Inhalation	Sprague-Dawley Rats	10 ppm 25 ppm 50 ppm 100 ppm 150 ppm for 12 months	98 weeks 98 weeks 98 weeks 98 weeks 98 weeks	negative negative negative positive positive	Maltoni, 1977; Maltoni et al., 1977
Inhalation	Sprague-Dawley Rats	75 ppm 200 ppm for 12 months	lifetime	negative negative	Viola and Caputo, 1977
Inhalation	Rats (Wister)	75 ppm 200 ppm for 12 months	lifetime	negative	Viola and Caputo, 1977
Inhalation	Rats (CD)	55 ppm	52 weeks	negative	Lee et al., 1978
Inhalation	Rats	25 ppm 75 ppm for 18 months	104 weeks	negative	Rampy et al., 1977

(Continued on next page)

TABLE VIII-1 (Continued)

Route	Species	Dose	Study Duration	Carcinogenic Response	Reference
Inhalation	Chinese Hamsters	25 ppm	74 weeks	negative	Maltoni, 1977; Maltoni et al., 1977
Oral (gavage)	Rats (BDIV)	50 mg/kg/day	120 weeks	negative	Ponomarkov and Tomatis, 1980
Oral (gavage)	Rats (Sprague-Dawley)	0.32 mg/kg/day	136 weeks	negative	Maltoni, 1977; Maltoni et al., 1977
		3.2 mg/kg/day		negative	
		6.4 mg/kg/day		negative	
		13 mg/kg/day		negative	
Oral (drinking water)	Rats (Sprague-Dawley)	7-9 mg/kg/day	104 weeks	negative	Rampy et al., 1977
		10-14 mg/kg/day		negative	Quast et al., 1983
		20-30 mg/kg/day		negative	
Oral (gavage)	Rats (F344)	1 mg/kg/day 5 mg/kg/day	104 weeks	negative	NTP, 1982
	Mice (B6C3F1)	1 mg/kg/day 5 mg/kg/day	104 weeks	negative	NTP, 1982
Subcutaneous	Swiss Mice			inactive as whole mouse initiator	Van Duuren et al., 1979
		121 mg	single dose	active as initiator with phorbol myristate acetate	

1,1-DCE has been tested in a number of short-term tests, some of which are considered to be useful in predicting mutagenic potential and also assisting in the evaluation of carcinogenic potential. It was mutagenic to bacteria in the presence, but not in the absence, of an exogenous metabolic activation system (Bartsch et al., 1975; Griem et al., 1975; Simmon et al., 1977; Jones and Hathway, 1978c; Simmon and Tardiff, 1979). It also induced point mutations and mitotic gene conversions in S. cerevisiae, but only after metabolic activation (Bronzetti et al., 1981).

1,1-DCE was not mutagenic in the dominant lethal test in CD-1 mice exposed by inhalation to 1,1-DCE at 40, 120 or 200 mg/m^3 for 6 hr/day for 5 days (Anderson et al., 1977). It also was not active in V79 Chinese hamster cells in the presence of 15,000 g liver supernatant from phenobarbital-treated rats and mice (Drevon and Kuroki, 1979), nor did it produce chromosomal aberrations in cytogenetic analyses of bone marrow cells following ip injections (Cerna and Kypenova, 1977 Abst.).

Reitz et al. (1980) showed that 1,1-DCE alkylated DNA in the liver and kidney of both rats and mice, but only to a slight degree after 6 hr inhalation exposures of 10 or 50 ppm. The highest degree of alkylation occurred in the kidney of mice at the higher dose. In measuring DNA repair, the only statistically significant increase caused by 1,1-DCE was that occurring in the kidney of mice exposed at 50 ppm.

On the basis of the data available to date, IARC (1983) concluded that there is sufficient evidence to state that 1,1-DCE is mutagenic. Earlier, IARC (1979) had stated that the available experimental evidence indicates that the compound produces malignant tumors in mice and rats and that some of the tumors are similar to those produced by vinyl chloride. IARC said that this evidence is, however, limited by the fact that it is based partly on studies which were in progress. A reevaluation will be made after IARC has reviewed the data of Maltoni et al. (1985), the Dow study and the NTP gavage bioassay. IARC's assessment of the available human data stated that they were not adequate to permit assessment of 1,1-DCE's carcinogenic potential in the human (IARC, 1983).

EPA recently finalized guidelines for the assessment of mutagenic risk (U.S. EPA, 1986a). These guidelines are designed to address heritable (germ cell) mutagenic risk, not somatic cell risk. The Office of Drinking Water (ODW), in a preliminary application of these guidelines, feels that there would exist limited evidence of human heritable risk following exposure to 1,1-DCE. ODW has asked the Reproductive Effects Assessment Group/Office of Health and Environmental Assessment to review and comment on ODW's assessment.

EPA also recently published final guidelines for carcinogen risk assessment (U.S. EPA, 1986b). These guidelines identify a five-level weight of evidence classification scheme. Applying the proposed guidelines, ODW determined that the available data on the mutagenic and carcinogenic potential of 1,1-DCE directs the characterization of its carcinogenic potential into Group C: Possible Human Carcinogen.

Group C is proposed to include agents with limited evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence: (a) definitive malignant tumor response in a single well-conducted experiment; (b) marginal tumor response in studies having inadequate design or reporting, (c) benign, but not malignant, tumors with an agent showing no response in a variety of short-term tests for mutagenicity, and (d) marginal responses in a tissue known to have a high and variable background rate.

1,2-Dichloroethylenes. Neither isomer has been tested for carcinogenic potential. Therefore, it is not possible to make any judgment on the possible human cancer risk of these two chemicals.

Neither cis- nor trans-1,2-DCE was mutagenic when assayed with *E. coli* at similar concentrations used for 1,1-DCE (Griem et al., 1975). However, cis-1,2-DCE was found to be mutagenic in the host-mediated assay using *Salmonella* tester strains in mice, but trans-1,2-DCE was not (Cerna and Kypenova, 1977 Abst.). These authors also reported that only the cis-isomer, of the three tested, produced chromosomal aberrations in bone marrow cells following intraperitoneal injections. Clearly, more studies must be completed before reaching conclusions on the mutagenic and carcinogenic potentials of the 1,2-isomers of DCE.

D. Quantification of Carcinogenic Effects

1,1-Dichloroethylene. Qualitative and quantitative assessments of the carcinogenic potential of 1,1-DCE are complicated by the fact that the only positive data -- mammary tumors in female rats and mice and kidney adenocarcinomas in mice (Maltoni, 1977) -- have become recently finalized (Maltoni et al., 1985).

On the basis of the preliminary data from the study using mice (Maltoni, 1977), the EPA Carcinogen Assessment Group calculated estimated incremental excess cancer risk associated with exposure to 1,1-DCE in drinking water (U.S. EPA, 1984). Assuming consumption of 2 liters of water by a 70-kg individual, it was estimated that exposure to 0.24 ug/L 1,1-DCE over a lifetime would result in a one in a million risk rate (10^{-6}). Risks of 10^{-5} and 10^{-4} were estimated if exposure occurred at 2.4 or 24 ug/L, respectively.

IARC (1983) reported that the data were inadequate to assess the carcinogenic potential in humans, but that it would reevaluate this assessment after reviewing the rat drinking water study (Rampy et al., 1977; Quast et al., 1983), the NTP gavage bioassays (NTP, 1982) and the Maltoni et al. (1985) studies.

Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), 1,1-DCE may be classified in Group C: Possible Human Carcinogen. Group C includes agents with limited evidence of carcinogenicity in animals in the absence of human data.

cis- or trans-1,2-Dichloroethylene. There are no data available which describe the carcinogenic potential of cis- or trans-1,2-DCE.

E. Summary

Tables VIII-2 through VIII-4 summarize the HA values calculated on the basis of non-carcinogenic endpoints, and the estimated excess cancer risk calculated using the linearized multistage model.

Table VIII-2

Summary of Quantification of Toxicological Effects for 1,1-Dichloroethylene

Value	Drinking Water Concentration	Reference
One-day HA for 10-kg child	2.0 mg/L	Chieco et al. (1981)
Ten-day HA for 10-kg child	1.0 mg/L[a]	Rampy et al. (1977)
Longer-term HA for 10-kg child	1.0 mg/L	Rampy et al. (1977)
Longer-term HA for 70-kg adult	3.5 mg/L	Rampy et al. (1977)
DWEL for 70-kg adult	0.35 mg/L	Quast et al. (1983)
Excess cancer risk		Maltoni (1977)
10^{-4}	24 ug/L	
10^{-5}	2.4 ug/L	
10^{-6}	0.24 ug/L	

[a] Due to the absence of appropriate data, the Longer-term HA for the 10-kg child is taken to be a conservative estimate of the Ten-day HA for the 10-kg child.

Table VIII-3

Summary of Quantification of Toxicological Effects for cis-1,2-Dichloroethylene

Value	Drinking Water Concentration	Reference
One-day HA for 10-kg child	4.0 mg/L	Jenkins et al. (1972)
Ten-day HA for 10-kg child	3.0 mg/L[a]	McCauley et al. (1990)
Longer-term HA for 10-kg child	3.0 mg/L	McCauley et al. (1990)
Longer-term HA for 70-kg adult	11.0 mg/L	McCauley et.al. (1990)
DWEL for 70-kg adult	0.35 mg/L	McCauley et al. (1990)

[a] Due to the absence of appropriate data, the Longer-term HA for the 10-kg child is taken to be a conservative estimate of the Ten-day HA for the 10-kg child.

Table VIII-4

Summary of Quantification of Toxicological Effects for trans-1,2-Dichloroethylene

Value	Drinking Water Concentration	Reference
One-day HA for 10-kg child	20.0 mg/L	Freundt et al. (1977)
Ten-day HA for 10-kg child	2.0 mg/L	Barnes et al. (1985)
Longer-term HA for 10-kg child	2.0 mg/L	Barnes et al. (1985)
Longer-term HA for 70-kg adult	6.0 mg/L	Barnes et al. (1985)
DWEL for 70-kg adult	0.6 mg/L	Barnes et al. (1985)

IX. REFERENCES

ACGIH. 1980. American Council of Government Industrial Hygienists. TLVs. Threshold limit values for chemical substances and physical agents in the workroom environment. Cincinnati, OH.

Andersen, M.E. and L.J. Jenkins, Jr. 1977. Oral toxicity of 1,1-dichloroethylene in the rat: Effects of sex, age and fasting. Environ. Hlth. Perspect. 21:157-163.

Andersen, M.E., R.A. Jones and L.J. Jenkins, Jr. 1977. Enhancement of 1,1-dichloroethylene toxicity by pretreatment of fasted male rats with 2,3-epoxypropan-1-ol. Drug Chem. Toxicol. 1:63-74.

Andersen, M.E., R.A.Jones and L.J. Jenkins, Jr. 1978. The acute toxicity of single, oral doses of 1,1-dichloroethylene in the fasted, male rat: Effect of induction and inhibition of microsomal enzyme activities on mortality. Toxicol. Appl. Pharmacol. 46:227-234.

Andersen, M.E., J.E. French, M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. 1979a. Saturable metabolism and the acute toxicity of 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 47:385-393.

Andersen, M.E., M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. 1979b. The use of inhalation techniques to assess the kinetic constants of 1,1-dichloroethylene metabolism. Toxicol. Appl. Pharmacol. 47:395-409.

Andersen, M.E., M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. 1980a. Determination of the kinetic constants for metabolism of inhaled toxicants *in vivo* using gas uptake measurements. Toxicol. Appl. Pharmacol. 54:100-116.

Andersen, M.E., O.E. Thomas, M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. 1980b. The significance of multiple detoxification pathways for reactive metabolites in the toxicity of 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 52:422-432.

Anderson, D., M.C.E. Hodge and I.F.H. Purchase. 1977. Dominant lethal studies with the halogenated olefins vinyl chloride and vinylidene chloride in male CD-1 mice. Environ. Hlth. Perspect. 21:71-78.

Bahlman, L.J., V. Alexander, P.F. Infante, J.K. Wagoner, J.M. Lane and E. Bingham. 1979. Vinyl halides: Carcinogenicity. vinyl bromide, vinyl chloride and vinylidene chloride. Joint NIOSH/OSHA Current Intelligence Bulletin No. 28. Am. Ind. Hyg. Assoc. J. 40:A30-A40.

Barnes, D.W., V.M. Sanders, K.L. White, G.M. Shopp and A.E. Munson. 1985. Toxicology of trans-1,2-dichloroethylene in the mouse. Drug Chem. Toxicol. 8:373-392.

Barr, R.F. and H. Watts. 1972. Diffusion of some organic and inorganic compounds in air. J. Chem. Eng. Data 17:45-46.

Bartsch, H. 1976. Mutagenicity tests in chemical carcinogenesis. IARC Sci. Publ. 13:229-240.

Bartsch, H., C. Malaveille, A. Barbin and G. Planche. 1979. Mutagenic and alkylating metabolites of halo-ethylenes, chlorobutadienes and dichlorobutenes produced by rodent or human liver tissues. Evidence for oxirane formation by P450-linked microsomal mono-oxygenases. Arch. Toxicol. 41:249-277.

Bartsch, H., C. Malaveille and R. Montesano. 1976. The predictive value of tissue-mediated mutagenicity assays to assess the carcinogenic risk of chemicals. IARC Sci. Publ. 12:467-491.

Bartsch, H., C. Malaveille, R. Montesano and L. Tomatis. 1975. Tissue-mediated mutagenicity of vinylidene chloride and 2-chlorobutadiene in Salmonella typhimurium. Nature 255:641-643.

Bonse, G., T. Urban, D. Reichert and D. Henschler. 1975. Chemical reactivity, metabolic oxirane formation and biological reactivity of chlorinated ethylenes in the isolated perfused rat liver preparation. Biochem. Pharmacol. 24:1829-1834.

Brodzinsky, R. and H.B. Singh. 1982. Volatile organic chemicals in the atmosphere: An assessment of available data. Prepared by SRI International, Menlo Park, CA, for Environmental Sciences Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC. Contract No. 68-02-3452.

Bronzetti, G., C. Bauer, C. Corsi, C. Leporini, R. Nieri and R. del Carratore. 1981. Genetic activity of vinylidene chloride in yeast. Mutat. Res. 89:179-185.

Broser, F., D. Henschler and H.C. Hopf. 1970. Chlorierte acetylene als ursache einer irreparablen trigeminusstorung dei zwei patienten. Dtsch. Z. Nervenheilk. 197:163-170.

Carlson, G.P. and G.C. Fuller. 1972. Interaction of modifiers of hepatic microsomal drug metabolism and the inhalation toxicity of 1,1-dichloroethylene. Res. Commun. Chem. Pathol. Pharmacol. 4:553-560.

Cerna, M. and H. Kypenova. 1977. Mutagenic activity of chloroethylenes analysed by screening system tests. Mutat. Res. 46:214-215 (Abst).

Chieco, P., M.T. Moslen and E.S. Reynolds. 1981. Effect of administrative vehicle on oral 1,1-dichloroethylene toxicity. Toxicol. Appl. Pharmacol. 57:146-155.

Chieco, P., M.T. Moslen and E.S. Reynolds. 1982. Histochemical evidence that plasma and mitochondrial membranes are primary foci of hepatocellular injury caused by 1,1-dichloroethylene. Lab. Invest. 46:413-421.

CFR. 1981. Code of Federal Regulations. Title 21. Food and Drugs. Parts 175 and 177. Office of the Federal Register, National Archives and Record Service, Washington, DC. pp. 144-151, 160, 183.

Costa, A.K. and K.M. Ivanetich. 1982. The 1,2-dichloroethylenes: Their metabolism by hepatic cytochrome P-450 *in vitro*. Biochem. Pharmacol. 31:2093-2102.

Dallas, C.E., F.W.Weir, S. Feldman, L. Putcha and J.V. Bruckner. 1983. The uptake and disposition of 1,1-dichloroethylene in rats during inhalation exposure. Toxicol. Appl. Pharmacol. 68:140-151.

De Ceaurriz, J., J.P. Desiles, P. Bonnet, B. Marignac, J. Muller and J.P. Guenier. 1983. Concentration-dependent behavioral changes in mice following short-term inhalation exposure to various industrial solvents. Toxicol. Appl. Pharmacol. 67:383-389.

DeLassus, P.T. and D.D. Schmidt. 1981. Solubilities of vinyl chloride and vinylidine chloride in water. J. Chem. Eng. Data 26:274-276.

Drevon, C. and T. Kuroki. 1979. Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells. Mutat. Res. 67:173-182.

Filser, J.G. and H.M. Bolt. 1979. Pharmacokinetics of halogenated ethylenes in rats. Arch. Toxicol. 42:123-136.

Filser, J.G. and H.M. Bolt. 1980. Characteristics of haloethylene-induced acetonemia in rats. Arch. Toxicol. 45:109-116.

Filser, J.G., H.M. Bolt, K. Kimmich and F.A. Bencsath. 1978. Exhalation of acetone by rats on exposure to trans-1,2-dichloroethylene and related compounds. Toxicol. Lett. 2:247-252.

Filser, J.G., P. Jung and H.M. Bolt. 1982. Increased acetone exhalation induced by metabolites of halogenated C_1 and C_2 compounds. Arch. Toxicol. 49:107-116.

Fishbein, L. 1979. Potential halogenated industrial carcinogenic and mutagenic chemicals. I. Halogenated unsaturated hydrocarbons. Sci. Total Environ. 11:111-161.

Forkert, P.G., E.M. Custer, A.J. Alpert, G.A.S. Ansari and E.S. Reynolds. 1982. Lactate dehydrogenase activity in mouse lung following 1,1-dichloroethylene: Index of airway injury. Exp. Lung Res. 4:67-77.

Forkert, P.G. and E.S. Reynolds. 1982. 1,1-Dichloroethylene-induced pulmonary injury. Exp. Lung Res. 3:57-68.

FRDS. 1983. Federal Reporting Data System. Facilities and population served by primary water supply source (FRDS07), April 19, 1983. U.S. Environmental Protection Agency, Washington, DC.

Freundt, K.J., G.P. Liebaldt and E. Lieberwirth. 1977. Toxicity studies on trans-1,2-dichloroethylene. Toxicology 7:141-153.

Freundt, K.J. and J. Macholz. 1978. Inhibition of mixed function oxidases in rat liver by trans- and cis-1,2-dichloroethylene. Toxicology 10:131-139.

Gage, J.C. 1970. The subacute inhalation toxicity of 109 industrial chemicals. Br. J. Ind. Med. 27:1-18.

Galli, A., C. Bauer, G. Bronzetti, C. Corsi, R. Del Carratore, R. Nieri and M. Paolini. 1982a. The genetic activity of 1,2-dichloroethylene. a). In vitro study. Boll. Soc. It. Biol. Sper. 58:860-863.

Galli, A., C. Bauer, G. Bronzetti, C. Corsi, R. Del Carratore, R. Nieri and M. Paolini. 1982b. The genetic activity of 1,2-dichloroethylene. b). In vivo study. Boll. Soc. It. Biol. Sper. 58:860-863.

Going, J.E. and J.L. Spigarelli. 1977. Environmental monitoring near industrial sites: vinylidene chloride. Prepared by Midwest Research Institute, Kansas City, MO, for U.S. Environmental Protection Agency. EPA-560/6-77-026. Cited in Brodzinsky and Singh 1982.

Greim, H., G. Bonse, Z. Radwan, D. Reichert and D. Henschler. 1975. Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. Biochem. Pharmacol. 24:2013-2017.

Groves, J.T. and R.S. Myers. 1983. Catalytic asymmetric epoxidations with chiral iron prophyrins. J. Am. Chem. Soc. 105:5791-5796.

Guyton, A.C. 1947. Measurement of the respiratory volumes of laboratory animals. Am. J. Physiol. 150:70-77.

Hamada, N. and R.E. Peterson. 1977. Effect of chlorinated aliphatic hydrocarbons on excretion of protein and electrolytes by rat pancreas. Toxicol. Appl. Pharmacol. 39:185-194.

Hardie, D.W.F. 1964. Dichloroethylenes. In: Mark, H.F., J.J. McKetta, Jr., D.F. Othmer, eds. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., Wiley-Interscience, New York, NY. Vol. 5. pp. 178-183.

Harkness, J.E. and J.U. Agner. 1983. The Biology and Medicine of Rabbits and Rodents. 2nd ed., Lea and Fibiger, Philadelphia, PA. p. 46.

Hathway, D.E. 1977. Comparative mammalian metabolism of vinyl chloride and vinylidene chloride in relation to oncogenic potential. Environ. Hlth. Perspect. 21:55-59.

Hayes, J.R., L.W. Condie, J.L. Egle and J.F. Borzelleca. 1987. The acute and subchronic toxicity in rats of trans-1,2-dichloroethylene in drinking water. J. Am. Coll. Toxicol. 6:471-478.

Henschler, D. 1977. Metabolism and mutagenicity of halogenated olefins--a comparison of structure and activity. Environ. Hlth. Perspect. 21:61-64.

Henschler, D. and G. Bonse. 1977. Metabolic activation of chlorinated ethylenes: Dependence of mutagenic effect on electrophilic reactivity of the metabolically formed epoxides. Arch. Toxicol. 39:8-12.

Henschler, D., G. Bonse and H. Greim. 1976. Carcinogenic potential of chlorinated ethylenes. Tentative molecular rules. IARC Sci. Publ. 13:171-175.

Henschler, D., F. Broser and H.C. Hopf. 1970. "Polyneuritis cranialis" durch vergiftung mit chloriertan acetylenen beim umgang mit vinylidenchlorid-copolymeren. Arch. Toxicol. 26:62-75.

Hewitt, W.R., and G.L. Plaa. 1983. Dose-dependent modification of 1,1-dichloroethylene toxicity by acetone. Toxicol. Lett. 16:145-172.

Horsely, L.H. 1947. Table of azeotropes and nonazeotropes. Ind. Engin. Chem., Anal. Chem. 19:508, 509, 518, 520, 586, 599, 600.

Hushon, J., and M. Kornreich. 1976. Air pollution assessment of vinylidene chloride. U.S. Environmental Protection Agency Contract No. 68-02-1495.

IARC. 1979. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risk of chemicals to humans. Some monomers, plastics and synthetic elastomers, and acrolein. IARC Monograph. 19:439-459.

IARC. 1983. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks of chemicals to humans. Chemicals, industrial processes and industries associated with cancer in humans. IARC monographs, Volumes 1 to 19. IARC monographs supplement 4. pp. 262-264.

ICRP. 1975. International Commission on Radiological Protection. Report of the task group on reference man. ICRP Publication 23. New York: Pergamon Press.

Irish, D.D. 1963. Vinylidene chloride. In: F.A. Patty (ed), Industrial Hygiene and Toxicology. 2nd ed. Vol. II. John Wiley and Sons, Inc., New York. pp. 1305-1309.

Jackson, N.M., W.J. Al-Hassan and R.B. Conolly. 1982. The nephrotoxicity of 1,2-dichloroethane and 1,1-dichloroethylene in male Sprague-Dawley rats. Toxicologist 2:127(Abst.).

Jaeger, J. and W. Stringer. 1972. Vinylidine chloride monomer. Safe handling guide. Dow Chemical USA. No. 102-232-72.

Jaeger, R.J. 1977. Effect of 1,1-dichloroethylene exposure on hepatic mitochondria. Res. Commun. Chem. Pathol. Pharmacol. 18:83-94.

Jaeger, R.J., R.B. Conolly and S.D. Murphy. 1973a. Diurnal variation of hepatic glutathione concentration and its correlation with 1,1-dichloroethylene inhalation toxicity in rats. Res. Commun. Chem. Pathol. Pharmacol. 6:465-471.

Jaeger, R.J., M.J. Trabelus and S.D. Murphy. 1973b. Biochemical effects of 1,1-dichloroethylene in rats: Dissociation of its hepatotoxicity from a lipoperoxidative mechanism. Toxicol. Appl. Pharmacol. 24:457-467.

Jaeger, R.J., R.B. Conolly and S.D. Murphy. 1974. Effect of 18 HR fast and glutathione depletion of 1,1-dichloroethylene-induced hepatotoxicity and lethality in rats. Exp. Mol. Pathol. 20:187-198.

Jaeger, R.J., R.B. Conolly and S.D. Murphy. 1975a. Short-term inhalation toxicity of halogenated hydrocarbons. Arch. Environ. Hlth. 30:26-31.

Jaeger, R.J., R.B. Conolly, E.S. Reynolds and S.D. Murphy. 1975b. Biochemical toxicology of unsaturated halogenated monomers. Environ. Hlth. Perspect. 11:121-128.

Jaeger, R.J., L.G. Shoner and L. Coffman. 1977a. 1,1-Dichloroethylene hepatotoxicity: Proposed mechanism of action and distribution and binding of ^{14}C radioactivity following inhalation exposure in rats. Environ. Hlth. Perspect. 21:113-119.

Jaeger, R.J., S. Szabo and L.J. Coffman. 1977b. 1,1-Dichlorethylene hepatotoxicity: Effect of altered thyroid function and evidence for the subcellular site of injury. J. Toxicol. Environ. Hlth. 3:545-555.

Jenkins, L.J., Jr., and M.E. Andersen. 1978. 1,1-Dichloroethylene nephrotoxicity in the rat. Toxicol. Appl. Pharmacol. 46:131-141.

Jenkins, L.J., Jr., M.J. Trabulus and S.D. Murphy. 1972. Biochemical effects of 1,1-dichloroethylene in rats. Comparison with carbon tetrachloride and 1,2-dichloroethylene. Toxicol. Appl. Pharmacol. 23:501-510.

Jones, B.K., and D.E. Hathway. 1978a. The biological fate of vinylidene chloride in rats. Chem.-Biol. Interact. 20:27-41.

Jones, B.K., and D.E. Hathway. 1978b. Differences in metabolism of vinylidene chloride between mice and rats. Br. J. Canc. 37:411-417.

Jones, B.K., and D.E. Hathway. 1978c. Tissue-mediated mutagenicity of vinylidene chloride in *Salmonella typhimurium* TA1535. Canc. Lett. 5:1-6.

Kallman, M.J., M.R. Lynch and M.R. Landauer. 1983. Taste aversion to several halogenated hydrocarbons. Neurobehav. Toxicol. Teratol. 5:23-27.

Krijgsheld, K.R., M.C. Lowe, E.G. Mimnaugh, M.A. Trush, E. Ginsburg and T.E. Gram. 1983. Lung-selective impairment of cytochrome P-450-dependent monooxygenases and cellular injury by 1,1-dichloroethylene in mice. Biochem. Biophys. Res. Commun. 110:675-681.

Lange, N.A., and G.M. Forker. 1961. Handbook of Chemistry. McGraw-Hill, New York. pp. 1484-1493.

Lee, C.C., J.C. Bhandari, J.M. Winston, W.B. House, R.L. Dixon and J.S. Woods. 1978. Carcinogenicity of vinyl chloride and vinylidene chloride. J. Toxicol. Environ. Hlth. 4:15-30.

Leibman, K.C., and E. Ortiz. 1977. Metabolism of halogenated ethylenes. Environ. Hlth. Perspect. 21:91-97.

Lentner, C. 1984. Geigy Scientific Tables. Vol. 3, 8th ed. Ciba-Geigy, Ltd., Basel. p. 209.

Letkiewicz, F., P. Johnston, C. Macaluso, R. Elder, W. Yu and C. Bason. 1983a. Occurrence of 1,1-dichloroethylene in drinking water, food and air. Prepared by JRB Associates, McLean, VA. for Office of Drinking Water, U.S. Environmental Protection Agency. Washington, DC. EPA Contract No. 68-01-6388.

Letkiewicz, F., P. Johnston, C. Macaluso, R. Elder, W. Yu and C. Bason. 1983b. Occurrence of 1,2-dichloroethylene in drinking water, food and air. Prepared by JRB Associates, McLean, VA. for Office of Drinking Water, U.S. Environmental Protection Agency. Washington, DC. EPA Contract No. 68-01-6388.

Ley, G.J.M., D.O. Hummel and C. Schneider. 1967. Gamma-radiation-induced polymerization of some vinyl monomers emulsion system. Adv. Chem. Ser. 66:184-202.

Liebler, D.C. and F.P. Guengerich. 1983. Olefin oxidation by cytochrome P-450: Evidence for group migration in catalytic intermediates formed with vinylidene chloride and trans-1-phenyl-1-butene. Biochemistry 22:5482-5489.

Liebler, D.C., M.J. Meredith and F.P. Guengerich. 1984. Reactive metabolites of vinylidene chloride: Characterization of covalent adducts formed with proteins and glutathione in microsomes and isolated hepatocytes. Canc. Res. 45:186-193.

MacDonald, T.L. 1982. Chemical mechanisms of halocarbon metabolism. CRC Crit. Rev. Toxicol. 11:85-120.

Maltoni, C. 1977. Recent findings on the carcinogenicity of chlorinated olefins. Environ. Hlth. Perspect. 21:1-5.

Maltoni, C., G. Cotti, L. Morisi and P. Chieco. 1977. Carcinogenicity bioassays of vinylidene chloride. Research plan and early results. Med. Lav. 68:241-262.

Maltoni, C., G. Lefemine, G. Cotti, P. Chieco and V. Patella. 1985. Experimental research on vinylidene chloride carcinogenesis. In: Archives of Research on Industrial Carcinogenesis. Volume III. C. Maltoni and M.A. Mehlman, eds. Princeton Scientific Publishers, Princeton, NJ. pp. 1-229.

Mansuy, D., L. Leclaire, M. Fontcave and M. Momenteau. 1984. Oxidation of monosubstituted olefins by cytochromes P-450 and heme models: Evidence for the formation of aldehydes in addition to epoxides and allylic alcohols. Biochem. Biophys. Res. Commun. 119:319-325.

Masuda, Y. and N. Nakayama. 1983. Protecive action of diethyldithiocarbamate and carbon disulfide against acute toxicities induced by 1,1-dichloroethylene in mice. Toxicol. Appl. Pharmacol. 71:42-53.

McCauley, P.T., M. Robinson, L.W. Condie and M. Purnell. 1990. The effects of subacute and subchronic oral exposure to cis-1,2-dichloroethylene in rats. (Unpublished data, HERL, Cincinnati, OH).

McKenna, M.J., P.G. Watanabe and P.J. Gehring. 1977. Pharmacokinetics of vinylidene chloride in the rat. Environ. Hlth. Perspect. 21:99-105.

McKenna, M.J., J.A. Zempel, E.O. Madrid and P.J. Gehring. 1978a. The pharmacokinetics of (^{14}C)-vinylidene chloride in rats following inhalation exposure. Toxicol. Appl. Pharmacol. 45:599-610.

McKenna, M.J., J.A. Zempel, E.O. Madrid, W.H. Braun and P.J. Gehring. 1978b. Metabolism and pharmacokinetic profile of vinylidene chloride in rats following oral administration. Toxicol. Appl. Pharmacol. 45:821-835.

Miller, R.E. and F.P. Guengerich. 1982. Oxidation of trichloroethylene by liver microsomal cytochrome P-450: Evidence for chlorine migration in a transition state not involving trichloroethylene oxide. Biochemistry 21:1090-1097.

Miller, R.E. and F.P. Guengerich. 1983. Metabolism of trichloroethylene in isolated hepatocytes, microsomes, and reconstituted enzyme systems containing cytochrome P-450. Canc. Res. 43:1145-1152.

Moore, L. 1980. Inhibition of liver-microsome calcium pump by _in vivo_ administration of CCl_4, $CHCl_3$, and 1,1-dichloroethylene (vinylidene chloride). Biochem. Pharmacol. 29:2505-2511.

Moore, L. 1982. 1,1-Dichlorethylene inhibition of liver endoplasmic reticulum calcium pump function. Biochem. Pharmacol. 31:1463-1465.

Munson, A.E., V.M. Sanders, K.A. Douglas, L.E. Sain, B.M. Kauffmann and K.L. White, Jr. 1982. _In vivo_ assessment of immunotoxicity. Environ. Hlth. Perspect. 43:41-52.

Murray, F.J., K.D. Nitschke, L.W. Rampy and B.A. Schwetz. 1979. Embryotoxicity and fetotoxicity of inhaled or ingested vinylidene chloride in rats and rabbits. Toxicol. Appl. Pharmacol. 49:189-202.

Nakajima, T., Y. Koyama and A. Sato. 1982. Dietary modification of metabolism and toxicity of chemical substances -- with special reference to carbohydrate. Biochem. Pharmacol. 31:1005-1011.

Nakajima, T. and A. Sato. 1979. Enhanced activity of liver drug-metabolizing enzymes for aromatic and chlorinated hydrocarbons following food deprivation. Toxicol. Appl. Pharmacol. 50:549-556.

NAS. 1977. National Academy of Sciences. Drinking Water and Health. Volume 1. National Academy Press. Washington, DC.

NIOSH. 1978. National Institute of Safety and Health. 1,2-Dichloroethylene. Registry of toxic effects of chemical substances. p. 563.

NIOSH. 1979. National Institute of Safety and Health. Criteria for a recommended standard -- Occupational exposure to vinyl halides. U.S. Department of Health, Education and Welfare. Washington, DC.

Norris, J.M. 1977. Toxicological and pharmacokinetic studies on inhaled and ingested vinylidene chloride in laboratory animals. Pap. Synth. Conf. 45-50 (Abst.).

NTP. 1982. National Toxicology Program. Carcinogenesis bioassay of vinylidene chloride (CAS No. 75-35-4) in F344 rats and $B6C3F_1$ mice (gavage study). U.S. HHS. PHS. NIH. NTP-80-2. NIH Publication No. 82-1784.

Ott, M.G., W.A. Fishbeck, J.C. Townsend and E.J. Schneider. 1976. A health study of employees exposed to vinylidene chloride. J. Occup. Med. 18:735-738.

Pearson, C.R. and G. McConnell. 1975. Chlorinated C_1 and C_2 hydrocarbons in the marine environment. Proc. R. Soc. London B. 189:305-332.

Pellizzari, E.D. 1978. Quantification of chlorinated hydrocarbons in previously collected air samples. U.S. Environmental Protection Agency, Research Triangle Park, NC. EPA-450/3-78-112. Cited in Brodzinsky and Singh, 1982.

Pellizzari, E.D., M.D. Erickson and R.A. Zweidinger. 1979. Formulation of a preliminary assessment of halogenated organic compounds in man and environmental media. Prepared by Research Triangle Institute, Research Triangle Park, NC, for U.S. Environmental Protection Agency. EPA-560/13-179-006. Cited in Brodzinsky and Singh, 1982.

Perry, R.H. and C.H. Chilton. 1973. Chemical Engineers' Handbook, 5th ed. McGraw-Hill, New York. pp. 13-36 to 13-42.

Ponomarkov, V., and I. Tomatis. 1980. Long-term testing of vinylidene chloride and chloroprene for carcinogenicity in rats. Oncology 37:136-141.

Prendergast, J.A., R.A. Jones, L.J. Jenkins, Jr. and J. Siegel. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 10:270-289.

Quast, J.F., C.G. Humiston, C.E. Wade, J. Ballard, J.E. Beyer, R.W. Schwetz and J.M. Norris. 1983. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride. Fund. Appl. Toxicol. 3:55-62.

Radding, S.B., D.H. Liu, H.L. Johnson and T. Mill. 1977. Review of environmental fate of selected chemicals. U.S. Environmental Protection Agency. Contract No. 68-01-2681. EPA-560/5-77-003.

Rampy, L.W., J.F. Quast, C.G. Humiston, M.F. Balmer and B.A. Schwetz. 1977. Interim results of two-year toxicological studies in rats of vinylidene chloride incorporated in the drinking water or administered by repeated inhalation. Environ. Hlth. Perspect. 21:33-43.

Ray, P. and L. Moore. 1982. 1,1-Dichloroethylene inhibition of liver microsomal calcium pump in vitro. Arch. Biochem. Biophys. 218:26-30.

Reichert, D. and D. Henschler. 1978. Uptake and hepatotoxicity of 1,1-dichloroethylene by the isolated blood-perfused rat liver. Int. Arch. Occup. Environ. Hlth. 41:169-178.

Reichert, D., H.W. Werner and D. Henschler. 1978. Role of liver glutathione in 1,1-dichloroethylene metabolism and hepatotoxicity in intact rats and isolated perfused rat liver. Arch. Toxicol. 41:169-178.

Reichert, D., H.W. Werner, M. Metzler and D. Henschler. 1979. Molecular mechanism of 1,1-dichloroethylene toxicity: Excreted metabolites reveal different pathways of reactive intermediates. Arch. Toxicol. 42:159-169.

Reichert, D. and H.W. Werner. 1978. Disposition and metabolism of [^{14}C]1,1-dichloroethylene after single oral administration in rats. Naunyn-Schmiedeberg's Arch. Pharmacol. 302(Suppl.), R-22 (Abst.).

Reitz, R.H., P.G. Watanabe, M.J. McKenna, J.F. Quast and P.J. Gehring. 1980. Effects of vinylidene chloride on DNA synthesis and DNA repair in the rat and mouse: A comparative study with dimethylnitrosamine. Toxicol. Appl. Pharmacol. 52:357-370.

Reynolds, E.S. and M.T. Moslen. 1977. Damage to hepatic cellular membranes by chlorinated olefins with emphasis on synergism and antagonism. Environ. Hlth. Perspect. 21:137-147.

Reynolds, E.S., M.T. Moslen, P.J. Boor and R.J. Jaeger. 1980. 1,1-Dichloroethylene hepatotoxicity. Time course of GSH changes and biochemical alterations. Am. J. Pathol. 101:331-341.

Reynolds, E.S., M.T. Moslen, S. Szabo, R.J. Jaeger and S.D. Murphy. 1975. Hepatotoxicity of vinyl chloride and 1,1-dichloroethylene. Role of mixed function oxidase system. Am. J. Pathol. 81:219-231.

Sato, A. and T. Nakajima. 1979. A structure-activity relationship of some chlorinated hydrocarbons. Arch. Environ. Hlth. 34:69-75.

Sato, A., T. Nakajima and Y. Koyama. 1983. Interaction between ethanol and carbohydrate on the metabolism in rat liver or aromatic and chlorinated hydrocarbons. Toxicol. Appl. Pharmacol. 68:242-249.

Shopp, G.M., V.M. Sanders, K.L. White and A.E. Munson. 1985. Humoral and cell-mediated immune status of mice exposed to trans-1,2-dichloroethylene. Drung Chem. Toxicol. 8:393-407.

Short, R.D., J.L. Minor, W.B. House, W. Marcus and C.C. Lee. 1976. Continuous inhalation of 1,1-dichloroethylene (DCE) by rats and mice during gestation. Pharmacologist 18:245 (Abst.).

Short, R.D., J.M. Winston, J.L. Minor, J. Seifter and C.C. Lee. 1977a. Effect of various treatments on toxicity of inhaled vinylidene chloride. Environ. Hlth. Perspect. 21:125-129.

Short, R.D., J.M. Winston, J.L. Minor, C.B. Hong, J. Seifter and C.C. Lee. 1977b. Toxicity of vinylidene chloride in mice and rats and its alteration by various treatments. J. Toxicol. Environ. Hlth. 3:913-921.

Short, R.D., J.L. Minor, J.M. Winston and C.C. Lee. 1977c. A dominant lethal study in male rats after repeated exposures to vinyl chloride or vinylidene chloride. J. Toxicol. Environ. Hlth. 3:965-968.

Siegel, J., R.A. Jones, R.A. Coon and J.P. Lyon. 1971. Effects on experimental animals of acute, repeated and continuous inhalation exposures to dichloroacetylene mixtures. Toxicol. Appl. Pharmacol. 18:168-174.

Siegers, C.P., K. Heidbuchel and M. Younes. 1983. Influence of alcohol, dithiocarb and (+)catechin on the hepatotoxicity and metabolism of vinylidene chloride in rats. J. Appl. Toxicol. 3:90-95.

Siegers, C.P., M. Younes and G. Schmitt. 1979. Effects of dithiocarb and (+) cyanidanol-3 on the hepatotoxicity and metabolism of vinylidene chloride in rats. Toxicology 15:55-64.

Siletchnik, L.M. and G.P. Carlson. 1974. Cardiac sensitizing effects of 1,1-dichloroethylene: Enhancement by phenobarbital pretreatment. Arch. Int. Pharmacodyn. Ther. 210:359-364.

Simmon, V.F., K. Kauhanen and R.G. Tardiff. 1977. Mutagenic activity of chemicals identified in drinking water. Dev. Toxicol. Environ. Sci. 2:249-258.

Simmon, V.F. and R.G. Tardiff. 1978. The mutagenic activity of halogenated compounds found in chlorinated drinking water. Water Chlorination: Environ. Impact Hlth. Eff. Proc. Conf. 2:417-431.

Szabo, S., R.J. Jaeger, M.T. Moslen and E.S. Reynolds. 1977. Modification of 1,1-dichloroethylene hepatotoxicity by hypothyroidism. Toxicol. Appl. Pharmacol. 42:367-376.

Theiss, A.M., R. Frentzel-Beyme and E. Penning. 1977. Mortality study of vinylidene chloride exposed persons in BASF. Proceedings of 5th Medichem. Congr. San Francisco, 1977. Cited in Ponomarkov, V., and I. Tomatis. 1980. Long-term testing of vinylidene chloride and chloroprene for carcinogenicity in rats. Oncology 37:136-141.

Thurman, G.B., B.G. Simms, A.L. Goldstein and D.J. Kollan. 1978. The effects of organic compounds used in the manufacture of plastics on the responsivity of murine and human lymphocytes. Toxicol. Appl. Pharmacol. 44:617-641.

U.S. Environmental Protection Agency. 1975. Preliminary assessment of suspected carcinogens in drinking water. Report to Congress. Office of Water Supply, Washington, DC. pp. 9-11, I-13, I-16.

U.S. Environmental Protection Agency. 1976. Vinylidene chloride monomer emissions from the monomer, polymer and polymer processing industries. Report by A.D. Little, Inc. Contract No. 68-02-1332. U.S. Environmental Protection Agency, Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1978. The Carcinogen Assessment Group's preliminary risk assessment on vinylidene chloride. May 30, 1978.

U.S. Environmental Protection Agency. 1980. Ambient water quality criteria for dichloroethylenes. Office of Water Regulations and Standards. Criteria and Standards Division, Washington, DC. EPA 440/5-80-041.

U.S. Environmental Protection Agency. 1981. Draft advisory opinion for 1,1-dichloroethylene (vinylidene chloride). Office of Drinking Water. October 7, 1981 (amended June 15, 1982).

U.S. Environmental Protection Agency. 1983. Memorandum from Dharm Singh to William Lappenbusch: "ODW September 15, 1983 Memorandum on Dichloroethylenes." September 20, 1983.

U.S. Environmental Protection Agency. 1986a. Guidelines for Mutagenicity Risk Assessment. Fed. Reg. 51(185):34006-34012. September 24.

U.S. Environmental Protection Agency. 1986b. Guidelines for Carcinogen Risk Assessment. Fed. Reg. 51(185):33992-34003. September 24.

U.S. Environmental Protection Agency. 1986c. U.S. EPA Office of Pesticides and Toxic Substances Gene-Tox Agent Registry. Computer printout, retrieved September 5, 1986. U.S. EPA, Washington, DC 20460.

Van Duuren, B.L., B.M. Goldschmidt, G. Loewengart, A.C. Smith, S. Melchionne, I. Seldman and D. Roth. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J. Natl. Canc. Inst. 63:1433-1439.

Viola, P.L. and A. Caputo. 1977. Carcinogenicity studies on vinylidene chloride. Environ. Hlth. Perspect. 21:45-47.

Warren, H.S. and B.E. Ricci. 1978. Vinylidene chloride. I. An overview. II. A literature collection. Oak Ridge National Laboratory, Oak Ridge, TN. ORNL/TIRC-77-3.

Watkins, J.B. and C.D. Klaassen. 1983. Chemically-induced alteration of UDP-glucuronic acid concentration in rat liver. Drug Metab. Disp. 11:37-40.

Wessling, R. and F.G. Edwards. 1970. In: Mark, H.F., J.J. McKetta, Jr., D.F. Othmer, eds. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., Wiley-Interscience, New York. Vol. 2i, pp. 275, 297-301.

Wessling, R. and F.G. Edwards. 1971. In: Encyclopedia of Polymer Science and Technology. Wiley, New York. Volume 14, p. 142.

Windholz, M., S. Budvari, L.Y. Stroumtsos and M.N. Fertig. (eds.) 1976. The Merck Index, 9th ed. Merck & Co., Inc., Rahway, NJ.

Younes, M. and C.P. Siegers. 1980. Lipid peroxidation as a consequence of glutathione depletion in rat and mouse liver. Res. Commun. Chem. Pathol. Pharmacol. 27:119-127.